ANNALS of ALLERGY

Published by
The American College of Allergists

Volume 18 September, 1960 Number 9

THE REPRODUCIBILITY OF INTRADERMAL SKIN TESTS: A CONTROLLED STUDY

PHILIP M. GOTTLIEB, M.D., F.A.C.A.,
SONIA STUPNIKER, M.D., F.A.C.A., and
S. I. ASKOVITZ, M.D.
Philadelphia, Pennsylvania

THE HISTORY of skin testing[1] as a diagnostic procedure in allergic states began in England in 1873, when C. H. Blackley demonstrated that hay fever patients formed urticarial wheals when scratch tested with pollens. In the ensuing four decades, systematic methods for scratch and intradermal testing in the diagnosis of allergic states were devised. By 1926, Fineman[2] suggested that asthma patients can be classified into three arbitrary groups according to their degree of sensitivity to scratch or intracutaneous tests. Thus the skin test began to be used not only for specific diagnosis, but also as a criterion of the degree of sensitivity and a guide to therapy. Colmes[3] suggested in 1932 that serial skin tests be used as a gauge for dosage in the treatment of hay fever. He demonstrated that in most cases positive skin tests diminished with therapy and that a parallelism existed between the skin reaction and the patient's clinical sensitivity to pollens.

Many allergists, however, noted that positive skin tests did not always indicate clinical allergy and that the skin test reaction frequently failed as a quantitative estimate of the degree of sensitization. In 1954 and 1955, Tuft[4,5] published several interesting articles regarding the reasons for changes in skin test reactions and pointed out that skin tests are not a re-

Presented in part at the Sixteenth Congress of The American College of Allergists, Bal Harbour, Florida, March 2, 1960.

Dr. Gottlieb is Attending Physician, Allergy Section, Albert Einstein Medical Center, Philadelphia, Pennsylvania; Associate in Medicine, University of Pennsylvania School of Medicine, Philadelphia, Pennsylvania.

Dr. Stupniker is an Adjunct in Allergy, Albert Einstein Medical Center, Philadelphia, Pennsylvania.

Dr. Askovitz is Medical Statistician, Albert Einstein Medical Center, Philadelphia, Pennsylvania.

liable indication of clinical progress, except after long-continued treatment with pollens which sometimes causes an appreciable decrease in reaction. Ogilvie[6] in 1954 discussed changes in skin test responsiveness in asthmatic patients over periods of two to seventeen years. He also found no relationship between changes in the clinical status of the patient and the variations in the skin test reactions.

In 1954, Herxheimer *et al*[7] questioned the technical reproducibility of skin tests. He studied the problem in twenty-one patients with respiratory allergies, employing the prick technique and the same twelve allergens in all cases. When retested on different days or at different times of the year, only three of twenty-one patients gave the same results to two consecutive tests, while the other eighteen showed considerable variation. Moreover, the correlation of skin test results with demonstrable clinical sensitivity and with results of bronchial testing was also poor.

It is a scientific axiom that a valid observation be reproducible or that the limitations of its failure to be reproducible be recognized. Every allergist has had the experience of retesting patients previously tested by others and finding a number of discrepancies in the reactions. Even in retesting his own patients, similar inconsistencies occur and are often attributed to actual immunological changes in the patients' reactivity, whether spontaneous or the result of elimination techniques or hyposensitization. But before one can evaluate the clinical significance of changes in skin tests reactivity, we must have a fairly accurate idea of the degree of reproducibility of the test in the hands of an average tester with standardized technique and allergenic extracts.

Since we found no comparable study of the technical reproducibility of the intradermal skin test without reference to its clinical or immunologic interpretation, the following controlled study was undertaken.

METHODS AND MATERIAL

Thirty-three patients suffering from a variety of allergic states were selected from the Allergy Clinic of the Albert Einstein Medical Center. The only basis of selection was that they had previously shown positive skin test reactions to two or more allergens, other than house dust, when tested by other staff members. They comprised twenty females and thirteen males, and ranged from eleven to sixty-six years in age, with an average of 36.2 years. The primary allergic diagnosis was allergic rhinitis in nine patients, seasonal hay fever in sixteen (including two seasons in nine), bronchial asthma in six, and urticaria in two patients. Secondary diagnoses were recorded in fifteen instances, chiefly hay fever. Nearly all were receiving hyposensitization therapy. Thirty of the patients returned 4.2 to 11.4 months later, after an average interval of 6.6 months. Accordingly, there were sixty-three visits in all. (In addition, four female subjects returned for a third visit within twenty-four hours of the onset of menstruation.)

At each of these visits, the same six tests were done in two rows of

TABLE I. INTRADERMAL TESTS:
SIXTY-THREE COMPARISONS FOR EACH ALLERGEN AT THE SAME VISIT

	Coca's Sol.	Histamine 1:10,000	Endo Dust 1:4,000	Oat 0.05N	Strong Selected	Weak Selected	Total: 378 Pairs	Total of 4 Allergens: 252 Pairs
Alike								
Both positive	5	62	49	29	55	43	243	176
Both negative	47	0	4	20	3	12	86	39
Total	52	62	53	49	58	55	329	215
Per cent	83	98	84	78	92	87	87.0	85.3
Different	11	1	10	14	5	8	49	37
Per cent	17	2	16	22	8	13	13.0	14.7

three tests on the outer surface of each upper arm. All patients were tested with Coca's solution, histamine diphosphate (equivalent to 1:10,000 of the histamine base), Endo house dust (1:4,000) and oat (0.05N), as well as two selected allergens to which the subject had reacted on earlier testing. The concentration of the extracts employed was that generally accepted for the substance involved. Once these were selected for the individual, the same were used for the second visit, but the order of placement on the arm was inverted in fifteen instances, and the tests were performed by two testers each using one arm at ten visits, to provide an opportunity for evaluating these variables. There were thirty individual patterns in the experimental design, each with a different placement of the tests, and the assignment was randomized. All testing was done by two of the authors.

The tests were done by the customary intradermal technique employing 26 gauge, short bevel needles and new asbestos-wrapped plunger syringes. Only one syringe was used for any one extract. The smallest detectable wheal was raised, requiring an estimated 0.01 or 0.02 cc. of fluid. The allergenic extracts were obtained from commercial sources, and the same vial was used throughout to obviate variations in dilution, standardization, or the potency of different lots.

The wheals and erythema were measured in millimeters, both longitudinally and laterally, after five, ten, fifteen, and twenty minutes. Pseudopodia were also recorded.

For the tabulation of the results, the following standards were arbitrarily used: any wheal up to but not including 5 x 5 mm was designated as negative; from 5 x 5 mm to 10 x 10 mm inclusive was considered 1+; from 10 x 10 mm to 15 x 15 mm was considered 2+; and so on up to 4+. A 4+ value was also assigned whenever there were pseudopods. The same basis was used for the erythema, but it was necessary to continue up to nine units.

RESULTS OF PAIRED COMPARISONS AT THE SAME VISIT

The experimental design permitted sixty-three pairs of comparisons of the reactions to each of six test substances, each tested on both arms. The results, including the number and percentage of whealing responses in agree-

ment and disagreement, are given in Table I. It will be noted that the pairs are not in complete agreement in 13.0 per cent of the tests or, if the figures for Coca's solution and histamine are eliminated, in 14.7 per cent. It should be pointed out that in this and subsequent tables, percentages based on totals less than 100 are rounded out to the nearest whole number.

It is worthy of emphasis that this is a fairly strict comparison, a single reading at even one of the four time intervals exceeding 5 mm in diameter requiring that the test be recorded as "positive." If we use a 2+ reaction, or 10 mm wheal, as the limit of discrimination, all the recorded disparities

TABLE II. INTRADERMAL TESTS:
PAIRED COMPARISONS AT THE SAME VISIT BY TYPES OF ALLERGENS

	Pollens	Epidermals	Molds	Foods	Total
No. cases	20	7	3	22	30†
No. allergens	2	6	2	14	24
No. pairs	46	14	5	61	126
Alike					
Both positive	41	11	2	44	100
Both negative	3	2	3	7	13
Total	44	13	5	51	113
Per cent	96	93	100	84	89.7
Different	2	1	0	10	13
Per cent	4*	7	0	16*	10.3

*Difference statistically significant ($p<0.05$).
†Note: Several subjects were tested with allergens in more than one category.

in this table disappear and are absorbed into the "both negative" line and yield a 100 per cent agreement between the pairs. Of the forty-nine pairs in disagreement, thirteen were reactions greater than 5 mm at only one of the four readings, and nine at only two of them. None of these discrepant readings exceeded 10 mm in diameter at any reading when the corresponding test on the opposite arm failed to exceed 5 mm in diameter at all four readings.

In Table I, the difference in percentages between paired tests in agreement and disagreement is statistically significant ($p < 0.05$); however, the differences between the four allergens are not.

If, in this table, the influence of using two testers simultaneously (each performing the tests on one arm) is eliminated, the percentage figures are not greatly changed. For example, instead of a total of 13.0 per cent disagreement, it would be 14.2 per cent.

At ten patient visits, the testing was done by two testers simultaneously, each performing the same six tests on one of the subject's arms. The results agreed (either positive or negative) in fifty-six out of sixty times. In four instances, the results for the same test substance on the same date were recorded as positive by one examiner and negative by the other. These discrepancies occurred in four different patients, so that even in these patients

TABLE III. INTRADERMAL TESTS: EFFECT OF POSITION (ON UPPER ARM)

	Coca's Sol.	Histamine 1:10,000	Endo Dust 1:4,000	Oat 0.05N	Strong Selected	Weak Selected	Total	Total: 4 Allergens
No. pairs	9	11	11	10	8	11	60	40
Alike								
Both positive	0	10	7	3	7	7	34	24
Both negative	8	0	1	4	0	3	16	8
Total	8	10	8	7	7	10	50	32
Per cent	89	91	73	70	88	91	83	80
Different	1	1	3	3	1	1	10	8
Per cent	11	9	27	30	12	9	17	20
Cumulative totals								
Top	1	70	49	19	62	32	233*	162*
Bottom	0	71	39	14	44	32	200*	129*

*Differences statistically significant ($p<0.05$).

five out of six readings were in agreement. It will be seen that the incidence of discrepancies for two testers was no greater, and actually somewhat less, than when one tester did all the tests, provided that the same extracts, the same testing techniques, and the same standards of reading were employed. It should also be pointed out that two of these apparent discrepancies each consisted of only 1+ reading at the five-minute period with Coca's solution. The other two instances of this sort both occurred with the "weak selected" allergen for the individual.

The two "selected" columns of Table I include 126 pairs of tests with twenty-four different allergens falling into four different groups. Table II presents the details. The differences between the groups (disregarding the molds which contained too few instances) are statistically significant at the 0.05 confidence limit. Accordingly, we are justified in concluding that tests with foods are less reliable than those with pollens or epidermals, an opinion that has long been held on clinical grounds.

We were interested in ascertaining whether, as is often held, the upper portion of the upper outer arm is more reactive than the lower portion. Table III presents the results of this comparison. In the upper portion of this table, it will be seen that 17 per cent of the pairs (20 per cent when only the four allergens are considered) were not in agreement when one test was done high on the upper arm and one on the lower portion. This is only slightly greater than the 13.0 (or 14.7) per cent which is the overall figure as shown in Table I, or the 12.3 per cent and 13.7 per cent when the same calculations are done for all the pairs whose positions were not inverted. This problem was attacked in a somewhat different way by totaling the accrued "scores," as shown at the bottom of the table. The difference between 233 and 200 is significant at the 0.05 level, so that we may say that the upper portion is slightly more reactive. This agrees with an earlier study of Bowman[8] who employed only ragweed pollen extract. However,

TABLE IV. INTRADERMAL TESTS:
CHANGES WITH TIME—THIRTY QUADRUPLE COMPARISONS OF
FOUR ALLERGENS, HISTAMINE, AND CONTROL

		Coca's Sol.	Histamine 1:10,000	Endo Dust 1:4,000	Oat 0.05N	Strong Selected	Weak Selected	Total: 180 Comp.	Total: 4 Allergens; 120 Comp.
All alike									
Both positive		1	29	20	10	24	18	102	72
Both negative		19	0	1	5	1	3	29	10
Total		20	29	21	15	25	21	131	82
Per cent		67	97	70	50	83	70	72.8	68.3
Different									
1st Visit	*2nd Visit*								
Negative	Positive	1	—	—	2	—	1	4	3
Positive	Negative	—	—	—	2	—	1	3	3
Unlike	Positive	—	—	2	1	2	2	7	7
Positive	Unlike	2	1	4	2	2	2	13	10
Unlike	Negative	1	—	1	4	1	2	9	8
Negative	Unlike	5	—	1	1	—	1	8	3
Unlike	Unlike	1	—	1	3	—	—	5	4
Total		10	1	9	15	5	9	49	38
Per cent		33	3	30	50	17	30	27.2	31.7

we disagree with her finding that histamine gives greater whealing in the lower portion of the upper arm since we did not find such a difference.

A similar totaling technique was used to compare the size of the wheals at the end of five, ten, fifteen, and twenty minutes. While there was no significant difference between the ten and fifteen minute totals, they both were significantly greater than the five or twenty minute totals.

By comparable statistical handling, we found no differences between the two arms for any of the test substances, nor for the total of all of them. Thus, with dust extract, the accrued "scores" were 261 for the right arm and 266 for the left; for all test substances, 1,028 and 996, respectively.

An attempt was made to correlate the degree of erythema with the whealing reaction, but the erythema was not found consistently proportional to the size of the wheal. Our clinical impression was that erythema was more likely to be related to the vasomotor status of patient and to skin pigmentation than any immunologic response.

RESULTS OF QUADRUPLE COMPARISONS AT TWO VISITS

Of primary interest is the potential variability of the skin test results over a period of time. Thirty of the subjects were retested from 126 to 343 days after the initial testing (mean, 197.8 days or approximately 6.6 months). Since each substance was tested in pairs at each of the two visits, this constitutes a quadruple comparison allowing a greater chance for discrepancies. This is reflected in the higher overall figure of 27.2 per cent of discrepancies, as shown in Table IV. The figures in this table may be compared to those in Table I. In this comparison, the results are classified as "all alike" only if all four tests with an allergen were in agreement, and as "different" if any one or more of the four tests failed to correspond

(either as positive or negative) at even one of the four readings. The term "unlike" indicates that the two tests at one of the visits were not in complete agreement by the standards outlined earlier.

In Table IV, it should be noted that of the forty-nine discrepancies in 180 quadruple comparisons, only seven were major disagreements in the sense that two positive results were obtained at one of the visits and two negative results at the other. Also of probable significance is the fact that these discrepancies were distributed among the allergens of lesser potency. If the figures for only the four allergens are taken into consideration, the percentage effect is not great, as shown in the last column.

TABLE V. INTRADERMAL TESTS: CHANGES WITH TIME—THIRTY QUADRUPLE COMPARISONS OF FOUR ALLERGENS, HISTAMINE, AND CONTROL: DIFFERENCES GREATER THAN TEN MM.

	Coca's Sol.	Histamine 1:10,000	Endo Dust 1:4,000	Oat 0.05N	Strong Selected	Weak Selected	Total: 180 Comp.	Total: 4 Allergens; 120 Comp.
All alike	30	29	28	29	28	27	171	112
Per cent	100	97	93	97	93	90	95.0	93.3
Different								
Negative to positive	—	—	—	1	—	—	1	1
One pair unlike, one pair positive	—	1	2	—	2	3	8	7
Total	0	1	2	1	2	3	9	8
Per cent	0	3	7	3	7	10	5.0	6.7

The fact that two testers were employed at some of the visits did not materially affect the results. Of fifteen quadruple comparisons in which two individuals performed the tests at one of the visits, discordant results occurred only four times, or 26.7 per cent.

Comparison of the recorded changes in reaction reveals no uniform tendency toward a weaker reaction at the second visit as compared with the first. This confirms the biologic stability of the extracts employed within the time limits of the study. This point was also evaluated by totaling the accrued "scores" at each of the visits. For all six test substances, they totaled 1,367 at the first visit and 1,438 at the second. Eliminating the tests with Coca's solution and histamine gave figures of 979 and 931, respectively, indicating no significant loss of potency as determined biologically within an average time period of 6.6 months.

If the data in Table IV are re-worked to indicate a discrepancy only if the wheal of one of the four tests exceeded 10 mm in diameter at one or more of the four readings, while at least one of the tests was less than 5 mm at all readings, considerably different results are obtained. These are shown in Table V, where it appears that only 5.0 per cent of all the comparisons are discordant. The significance of this, as well as of the comparable observations at a single visit, is considered below.

TABLE VI. INTRADERMAL TESTS: CHANGES WITH TIME—QUADRUPLE COMPARISONS OF "SELECTED" ALLERGENS

	Pollens	Epidermals	Molds	Foods	Total
No. cases	18	7	2	20	30†
No. allergens	2	6	2	12	22
No. comparisons	22	7	2	29	60
All alike					
All positive	19	5	1	17	42
All negative	1	1	1	1	4
Total	20	6	2	18	46
Per cent	91	86	100	62	77
Different					
Negative to positive	—	—	—	1	1
Positive to negative	—	—	—	1	1
One pair unlike, one pair positive	1	1	—	6	8
One pair unlike, one pair negative	1	—	—	3	4
Total	2	1	0	11	14
Per cent	9	14	0	38	23

†Note: Several subjects were tested with allergens in more than one category.

A more detailed analysis of the "strong selected" and "weak selected" columns of Table IV yields the findings given in Table VI. This comparison is again based on a 5 mm limit of variability between the positive whealing reaction and that less than 5 mm, considered as negative. It is once more apparent that food allergens give less reproducible results than the other groups, the differences being statistically significant. It should also be pointed out that nine of the fourteen discrepancies occurred with the weaker "selected" allergens, that is, with one of the patients' minor sensitivities.

At each visit, the indoor and outdoor temperatures and the barometric pressure were recorded, the latter data obtained through the courtesy of the Philadelphia Weather Bureau. The indoor temperatures varied too little to be useful in calculation. The extremes of outdoor temperatures were recorded as 19° and 86° F., but the greatest difference at the two visits of any one test subject was 59° F. The comparable figures for the barometric pressures were 29.31, 30.24 and 0.72 inches Hg. Within these limits, analysis of the effects of changes in temperature and barometric pressure on the results of skin tests revealed no consistent pattern.

An attempt was made to observe the effects of menstruation on cutaneous reactivity. Unfortunately, only four cases returned for a third visit on the first day of menses. No consistent pattern of the effect of menstruation on the skin test reactions could be noted at these visits. Admittedly, the number of test subjects was small.

DISCUSSION

Although the interpretation of intradermal skin tests may vary according to the tester or clinician, the testing technique and the recording of the results are fairly well standardized. The skin test reaction is generally gauged either

by measuring the diameters of the wheal and erythema, or the actual tracing of the size and shape of wheal and erythema on paper. Some less common methods are the use of Berkoff's[9] "cutometer" which consists of a celluloid film which has four round holes of 1, 1.5, 2, and 3 cm, used for measuring the sizes of the wheals which are then recorded as 1+ to 4+ reactions, or the "contour gauge" of Abramson and Gorin[10] which measures and records the increase in both the area of the wheal and its height. Wodehouse[9] suggested a rather interesting formula utilizing the size of both wheal and erythema to estimate the size of the skin reaction. Most authorities accept a 5 mm wheal as a weakly positive reaction or a ±. A wheal of 5 to 10 mm diameter is usually recorded as 1+, 10 to 15 mm as 2+, 15 to 20 mm 3+, and 20 mm or more or a wheal with pseudopodia as 4+.[11]

We were primarily interested in finding the lowest level of positive reactions at which we still obtained a high degree of reproducibility, and on the basis of our findings it appears that the level of 10 to 15 mm diameter is preferable to our original standard of 5 to 10 mm diameter as a 1+ reaction.

The optimum time for reading the test has been designated as fifteen to thirty minutes[12] or over twenty minutes.[11] Our experience suggests that skin reactions begin to fade after fifteen minutes and are best read between ten and fifteen minutes after injection.

We anticipated a perceptible reduction in the reproducibility of skin tests when two testers worked simultaneously and were gratified by the minimal effect actually found. Apparently adhering to the same standards of technique and recording of results overcomes the slight personal variant inherent in the work of different testers.

A review of the literature reveals a number of studies on the subject of the change in skin test reactions either after passage of time or following hyposensitization treatment or avoidance of the offending allergens. Ogilvie[6] followed the skin responses to common inhalant allergens in 209 asthmatic patients for two to seventeen years and found that skin responses were altered in ninety out of 209 or 43 per cent of the cases, but that the sensitivity changes had no relation to the clinical progress of the patient. In an analysis of the replies of 350 practicing allergists, Tuft[4] found polar opinions regarding the possibility of changes in skin test reactions. His own review of forty-eight cases of food allergies and seventy-eight cases of pollen sensitivities led him to the following conclusions: 1. Patients may acquire sensitization to new foods particularly after continued or prolonged contact. 2. Once sensitization has occurred as evidenced by a positive skin test it does not change as a result of either avoidance or allergic treatment. In pollen cases long and continued treatment may produce some slight decrease in the positive reaction. 3. Skin test reactions may decrease with advancing years, especially after the age of fifty to sixty years, because of the lessened skin reactivity.

Tuft's results were at great variance with those obtained by Colmes[3]

who found a diminution in skin test reactions in 91 per cent of treated pollen cases. Mathieson[1] agrees with Tuft, stating that skin tests to inhalants and pollens seldom become negative, whereas positive tests to foods may readily become negative if ingestion of these foods is avoided for a variable period. Peshkin[13] also found that positive food reactions fluctuated, and frequently spontaneously became negative.

Tuft's aphorism[14] that positive skin reactions may represent past, present, or future sensitivity has been accepted by most allergists, but of greater importance is his counsel that all positive reactions be checked at least once. He states that unless a positive reaction can be obtained repeatedly, it must be attributed to faulty technique or irritating extracts.

Our findings indicate that if maximum reproducibility of skin tests is desired, the criteria of interpretation of the skin tests must be more precise, and the weakly positive reactions, which in our hands were found to have a rather limited degree of reproducibility, might well be ignored. We feel that an important reason for the apparent change so frequently reported in skin test reactions to foods is explained by the "false positive" or the "unreproducible positive" reaction of the original food test.

Interesting observations on the cutaneous absorption during the menstrual cycle have been made by Seeberg[15] and Hard,[16] indicating a diminution or complete extinction of the whealing reaction prior to and on the first day of the period. They investigated various skin reactions of the delayed type, such as the tuberculin, Schick and Dick tests, and found them definitely decreased at the onset of menses as compared to other days of the menstrual cycle. Unfortunately we could not collect sufficient data on this subject, but in our relatively few cases we did not confirm any effect of menstruation on cutaneous reactivity.

No discussion of intradermal skin tests should omit consideration of dermographism which is described as an abnormal urticarial reaction to mechanical irritation, probably due to an unusual release of histamine by mast cells.[17] A dermographic skin will react with large wheals to controls of saline as well as allergenic substances.

Of the multiple factors governing cutaneous responsiveness, the role of the vasculature and the circulation has been reviewed in the classical study of Lewis[18] and of the lymphatics by Hudack and McMaster[19] and McMaster.[20] While the latter studies showed the rapidity of the entrance of intradermally injected material into superficial and frequently into the deeper lymphatics, the relative uniformity of wheal production by intradermal injection may be explained by the compression of the drainage channels by the wheal fluid, thereby interfering with the lymphatic transport. The observations of Bowman and Walzer[21] on the local state of hyporesponsiveness are not pertinent to our study, since they employed a passive transfer technique and retested the sensitized sites within a few weeks, rather than after several months. The statistical study of skin test reactions by Pabst, Boatner and Efron[22] was one of a series designed for the biologic standard-

ization of extracts, was carried out by the scratch technique, and employed only a single allergen, purified house dust extract. It yielded only peripheral and inadequate data regarding the consistency of patient responses to testing with this allergen. While they pointed out that the usual classification of skin reaction sizes is inappropriate for the statistical analysis of comparative tests, this does not apply to the present study, in which the reactions were measured in millimeters.

Finally, we would like to stress the fact that this study does not attempt to answer many important problems in the clinical application of intradermal skin tests. These include the techniques of preparing allergenic extracts, the question of optimum concentrations of extracts, the list of allergens to be employed in any case, the significance of late reactions, the changes of reactivity occurring over a period of years with or without specific therapy, and the crucial problem of the correlation of test results with true clinical sensitivity.

SUMMARY

A controlled study of intradermal skin tests in thirty-three patients at sixty-three visits using six tests on each arm revealed a lack of uniformity in results in only 13 per cent of the cases when wheals exceeding 5 mm in diameter were considered positive. When the level of discrimination was 10 mm or more, complete uniformity was demonstrated.

A repetition of the tests in thirty subjects after a mean interval of 6.6 months yielded a discrepancy of 27.2 per cent at the 5 mm level of discrimination and only 5.0 per cent at the 10 mm level.

Further analysis of the data indicated the following:

1. The skin test results obtained by two simultaneous testers were no more disparate than those obtained by one tester, when techniques and criteria of interpretation were uniform.

2. Foods gave definitely less consistent skin reactions than dust, pollens and epidermals.

3. Reactions tended to be greater after ten and fifteen minutes than after five or twenty minutes.

4. The upper portion of the upper arm was found to be slightly more reactive than the lower.

5. Within the average period of 6.6 months, the extracts showed no significant loss of whealing potency.

CONCLUSIONS

1. Intradermal skin tests possess a high degree of reproducibility when the following standards are observed:

   (a) Reactions should be considered positive only if the diameter of the test wheal exceeds that of the control wheal by 10 mm or more. At this level a minimum of unreproducible positives will be found.

   (b) Reactions should be read after ten or fifteen minutes when maximum whealing occurs.

2. Skin test reactions are somewhat stronger on the upper portion of the upper arm than on the lower.

3. Supposed "changes" in skin test reactivity of a given patient over a period of time should be evaluated in terms of the degree of demonstrated reproducibility and with consideration of uniformity of technique, extract standardization, and criteria of interpretation.

4. Precise standards of performance and interpretation of intradermal skin testing will eliminate much of the supposed variability.

REFERENCES

1. Mathieson, A.: Skin tests and their value in pediatric allergy. Pediat. Clin. North America, 1:929, 1954.
2. Fineman, A. H.: Studies in hypersensitiveness. XXV. A study of the degree of sensitivity of asthmatics to various atopens. J. Immunol., 12:191, 1926.
3. Colmes, A.: Serial skin tests as a guide in the treatment of hay fever. J. Allergy, 3:449, 1932.
4. Tuft, L., and Heck, V. M.: Studies in sensitization as applied to skin reactions. J. Allergy, 25:340, 1954.
5. Tuft, L., Heck, V. M., and Gregory, D. C.: Studies in sensitization as applied to skin test reactions. Influence of age upon skin reactivity. J. Allergy, 26:359, 1955.
6. Ogilvie, A. G.: Changes in skin response in asthma. Brit. M. J., 1:370, 1954.
7. Herxheimer, H., McInroy, P., Sutton, K. H., Utidjian, H. L., and Utidjian, H. M. D.: The evaluation of skin tests in respiratory allergy. Acta Allergol., 7:380, 1954.
8. Bowman, K. L.: Pertinent factors influencing comparative skin tests on the arm. J. Allergy, 7:39, 1935.
9. Cited by Hansel, F. K.: Clinical Allergy. pp. 291, 293, 294. St. Louis: C. V. Mosby, 1955.
10. Abramson, H. A., and Gorin, M. H.: Skin reactions: V. A contour gauge for measurement of height and breadth of allergic wheals. J. Allergy, 10:159, 1939.
11. Urbach, E., and Gottlieb, P. M.: Allergy. 2nd ed., pp. 165, 166. New York: Grune & Stratton, 1946.
12. Hansel, F. K.: Clinical Allergy. p. 296. St. Louis: C. V. Mosby, 1955.
13. Peshkin, M. M.: Pitfalls of the skin tests in allergy. J.A.M.A., 157:820, 1955.
14. Tuft, L.: Critical evaluation of skin tests in allergy diagnosis. J. Allergy, 14: 355, 1943.
15. Seeberg, G.: Cutaneous absorption during menstrual cycle. Acta Dermat.-Venereol., 30:231, 1950.
16. Hard, S.: Results of some skin tests in various phases of the menstrual cycle. Acta Dermat.-Venereol., 30:249, 1950.
17. Pillsbury, D. M., Shelley, W. B., and Kligman, A. M.: Dermatology. pp. 774, 1178. Philadelphia: W. B. Saunders Co., 1956.
18. Lewis, T.: The Blood Vessels of the Human Skin and Their Responses. London: Shaw & Sons, Ltd., 1927.
19. Hudack, S. S., and McMaster, P. D.: The lymphatic participation in human cutaneous phenomena; a study of the minute lymphatics in the living skin. J. Exper. Med., 57:751, 1933.
20. McMaster, P. D.: Lymphatic participation in cutaneous phenomena. Harvey Lectures, Series 37, pp. 227-268, 1942.
21. Bowman, K. L., and Walzer, M.: Studies in reaginic and histaminic wheals: I. The effects of reaginic and histaminic wheals upon the subsequent responsiveness of passively sensitized cutaneous sites. J. Allergy, 24:126, 1953.
22. Pabst, M. R., Boatner, C. H., and Efron, B. G.: Studies with antigens: V. Analysis of comparative skin reactions by means of the chi-square statistic. New Orleans M. & S. J., 93:142, 1940.

818 Medical Arts Center (Dr. Gottlieb)

BLOOD PROTEINS AND ELECTROLYTES IN ALLERGIC PATIENTS

JORGE RAUL VACCAREZZA, M.D.
Buenos Aires, Argentina

WITH A VIEW to investigating whether any permanent or transitory humoral modification exists which could explain the facility with which allergic patients contract sensitivities, we performed an electrophoretic study of the plasma proteins and the dosage of blood electrolytes. These examinations were performed simultaneously in order to coordinate the results obtained, and they were complemented with various routine tests.

CLINICAL MATERIAL

The dosages of blood proteins and electrolytes were simultaneously measured in forty respiratory allergic patients (thirty-three suffering from asthma and seven from pollenic rhinitis).

The patients were given a complete semiological examination, the respiratory frequency, inspiratory apnea time were determined and the amount of dyspnea present at the moment the tests were made was recorded.

The patients were first studied from an allergic point of view, and bacterial sensitivities were found in twenty-two patients; allergy to pollen in ten patients; common inhalants in thirteen patients; nemophyl fungi in four patients; hormonal allergy in five patients, and allergy to food in four patients.

In order that the results of the dosages of blood electrolytes would not be influenced by changes outside the study of allergic sensitivities, we classified the patients in two groups, (1) Purely allergic cases, and (2) those with superimposed sinal or bronchial infection. The first group consisted of thirty patients and the second of ten patients.

To obtain this classification we took into account the examination of the nasal secretions and expectoration, x-rays of the paranasal sinuses, erythro-sedimentation rate, leukocyte count and the histories of the patients insofar as superimposed infections were concerned. In order to avoid any extraneous influence on the values, the patients had not received corticoids, and all medication was stopped ten days before the tests began.

With a view to verifying any possible relationship between the degree of intensity of the clinical picture at the time examination took place and the values found, the patients were classified into the following groups: (1) those with no symptoms or signs of respiratory troubles, seven patients; (2) patients with some respiratory symptoms (nasal obstruction, a few sibilant rales) twenty-four patients; (3) patients with symptoms and signs

---

Dr. Vaccarezza is Chief of the Non-Tuberculous Respiratory Diseases Service of the Chair of Pathology and Clinical Tuberculosis of the Buenos Aires Faculty of Medicine.

of intense respiratory disturbances (subjective dyspnea, sibilant rales, decreased apnea time, and increased respiratory frequency) nine patients.

METHODS

Proteins

The electrophoretic study of serum proteins was performed using the SPINCO model R apparatus for electrophoresis with capacity for eight paper strips, thus allowing the carrying out of eight runs simultaneously.

The buffer used was a solution of tampon veronal-veronal sodium adjusted to pH 8.6 with Beckman's model G apparatus.

The blood samples were centrifuged and the serums obtained were placed by the Spinco special micropipette at the rate of 0.01 ml to each strip of paper. They were then submitted to electric separation for sixteen hours using a constant current of 5 milliamperes.

The strips were then dried in an oven at a temperature of 120-130° C for thirty minutes, coloring being carried out for six hours with a solution of bromophenol blue. The excess coloring was eliminated by two washings in 5 per cent acetic acid, and then fixation of the colored strips was performed using a fixing solution of 9 per cent sodium acetate in 10 per cent acetic acid. The slips were again dried in an oven heated to 120-130° C for fifteen minutes and submitted to ammonia fumes. The curves were made in the Spinco Analytrol, which is a densimeter with automatic tracings.

The values obtained were expressed in grammes per cent.

Electrolytes

Sodium and Potassium Dosage—Baird Associates' flame photometer was used for the dosages of sodium and potassium, and gave precise results. In order to assure exact results, the samples of blood were obtained under correct conditions. For this, Pyrex test tubes which had been washed previously with a sulfocromic mixture and rinsed in bidistilled water were used. The Pyrex syringes used were also washed in the same manner. All the glass material used was dried in the oven at 120° C.

The corresponding dilutions of the separated serums were made in tridistilled water and were analyzed in the flame photometer. The correct filters for sodium and potassium were used.

The values obtained were expressed in mg per cent and milliequivalents.

Calcium Dosage—For this we used Clark and Collip's classic procedure which is based on the fact that calcium is precipitated with ammonium oxalate and that the precipitate, after being washed with diluted ammonium solution, is dissolved in 21 per cent sulfuric acid, permanganovolumetry. The results were expressed in mg per cent.

Magnesium Dosage.—The magnesium dosage was effected with Morgulis' colorometer method. By this method, the calcium is previously separated

and precipitated in a 3 per cent ammoniac oxilate solution. It is then centrifuged, and in the floating liquid, separation of the magnesium to the state of magnesic, ammoniated phosphate, takes place. Once this has been centrifuged and washed, it is dissolved in sulphuric acid N. Then, in successive stages, molybdic acid solution, hydroquinone solution and carbosulfitic solution are added. The result is then read in Bausch & Lomb's Spectronic 20 photocolorometer in the 620 mu wave length.

TABLE I. STATISTICS

Infected Allergic Patients	Sodium	Potassium	Calcium	Magnesium	Plasma Chloride	Total Chloride	Globular Chloride
Normal (s. Houssay and Fawcett-Wynn)	330,5 ± 2,3 325,9 − 335,1	16,0 ± 1,11 13,7 − 18,2	10,2 ± 0,62 8,9 − 11,4	2,25 ± 0,32 1,6 − 2,8	365,65 ± 4,2 357 − 374	277 ± 3,70 270 − 300	180 ± 3,2 174 − 186
Purely allergic patients	320 ± 2,07** 315,7 − 324,1	19,3 ± 0,31** 16,5 − 22,7	10,28 ± 1,03 8,22 − 12,3	1,97 ± 0,047 1,88 − 2,05	340 ± 6,96** 326 − 354	296 ± 8,05 279 − 304	231 ± 5,46** 220 − 241,9
Infected allergic patients	324 ± 1,04* 322,9 − 326	18,4 ± 0,78 16,8 − 19,9	10,2 ± 0,09 10,2 − 10,1	2,09 ± 0,09 1,90 − 2,18	339 ± 6,43** 326 − 351	300 ± 7,99 285 − 316	231 ± 5,06** 220,8 − 241,1

Note: The first figures given include the standard error
The second figures are the fiduciary limits.
To evaluate the differences Student's t test was used.
* Significant difference for P=0,05
** Highly significant difference for P=0,01

Chloride Dosage.—Einsenman's modification of Van Slyke and Sondrey's method was used. This method is based on the fact that chloride precipitates in nitrate of silver to the strength of silver chloride in a strong nitric medium and destroys the organic material by adding permanganate of potassium while hot. The excess silver is sulfocyanide of potassium. The values obtained were again expressed in mg per cent.

RESULTS

In earlier studies performed by Drs. R. J. Bonacossa and J. A. Willson,[22,23] we made some observations which we now amplify and confirm by statistic analysis.

Proteins

The albumin showed no statistically significant variation in the purely allergic patients. In the infected ones, there was a diminution of albumin in 40 per cent of the cases but the statistics analysis did not show any variations.

Fractioning of the globulins has shown interesting variations. There was a marked and constant decrease of the α_1 globulin, both in the purely allergic patients and in the infected ones. Very low values were found, oscillating between 0.10 g and 0.28 g, in 72.5 per cent of the total cases; normal values were found in 27 per cent, but these were near the lowest limit

of what are considered normal values (0.31 g and 0.51 g). Statistical analysis showed *highly significant* diminution of the α_1 fraction. With respect to the α_1 fraction, this showed no change in the purely allergic patients but was found to be high in 40 per cent of the infected cases. Statistically this increase is significant.

The β globulin also showed variations, as it was found to be increased in 46 per cent of the purely allergic patients and 70 per cent of the infected cases. Statistical analysis showed *highly significant* variations.

TABLE II. STATISTICS

	Total Protein	Albumin				
Normal†	7,10 ± 0,064 6,98 − 7,22	3,70 ± 0,06 3,58 − 3,82	0,041 ± 0,019 0,38 − 0,44	0,65 ± 0,02 0,59 − 0,70	0,90 ± 0,025 0,85 − 0,95	1,44 ± 0,03 1,38 − 1,50
Purely allergic patients	7,00 ± 0,138 6,73 − 7,27	3,75 ± 0,13 3,49 − 4,01	0,26 ± 0,018** 0,23 − 0,29	0,60 ± 0,03 0,54 − 0,66	1,19 ± 0,046** 1,10 − 1,28	1,39 ± 0,071 1,25 − 1,53
Infected allergic patients	7,60 ± 0,33 6,94 − 8,26	3,92 ± 0,48 2,96 − 4,88	0,30 ± 0,019** 0,26 − 0,33	0,73 ± 0,049* 0,64 − 0,82	1,40 ± 0,14** 1,22 − 1,68	1,31 ± 0,17 0,97 − 1,65

†Values found in 20 normal adults.
Note: The first figures given include the standard error.
The second figures are the fiduciary limits.
To evaluate the differences Student's t test was used.
* Significant differences for P=0,05.
** Highly significant differences for P=0,01.

With respect to the gamma globulin, there was no noticeable change in the purely allergic cases, but a 40 per cent increase was found in the infected cases, although there were two cases of hypogammaglobulinemia (0.33 g per cent and 0.44 g per cent) among this latter type. These corresponded to chronically infected asthmatic patients who were resistant to active immunization.

Statistically, the gamma globulin did not show significant variations in these patients.

We tried to find out if any relationship existed between the intensity of the patients' symptoms at the time the electrophoretic test was made, and the values found, but there were no definite modifications which could be considered as directly influencing the values.

Electrolytes

We first of all considered the Plasma Na values and found subnormal values in nineteen patients. These were classified as follows: purely allergic patients fourteen (46.6 per cent), infected allergic patients five (45.4 per cent) of the total cases studied. Statistical analysis showed a *highly significant* diminution in Plasma Na in both types of patients.

Increased values in Plasma K were found in eleven out of twenty-eight pure allergic cases (39.2 per cent). Statistical analysis showed a *highly significant* increase in the purely allergic cases.

The Na/K ratio which is used for diagnostic purposes in suprarenal hypofunction has also been ascertained. In this endocrinal disturbance, the values are less than twenty-two, which is the co-efficient considered

TABLE III. VALUES OF THE PLASMA PROTEINS IN PURELY ALLERGIC PATIENTS
Given in gm. per cent

Purely Allergic Patients	Total Protein	Albumin					Total Globulin	Ind. Alb/Globulin
1.	6,40	2,97	0,24	0,85	2,02	0,32	3,43	0,86
2.	6,40	3,11	0,27	0,64	1,33	1,05	3,29	0,94
3.	6,40	2,34	0,24	0,65	1,20	1,47	3,56	0,69
4.	7,20	3,98	0,25	0,56	1,15	1,26	3,22	1,23
5.	7,00	4,28	0,15	0,51	0,96	1,10	2,72	1,57
6.	6,60	5,01	0,10	0,20	0,46	0,83	1,59	3,10
7.	6,00	2,78	0,35	0,61	0,89	1,37	3,22	0,86
8.	7,10	3,68	0,34	0,57	0,87	1,68	3,42	1,07
9.	8,80	4,75	0,17	0,62	1,25	2,01	4,05	1,17
10.	6,00	3,14	0,17	0,44	0,68	1,57	2,88	1,09
11.	6,60	3,73	0,23	0,48	0,82	1,34	2,87	1,29
12.	6,40	3,39	0,20	0,52	1,07	1,20	3,01	1,12
13.	7,80	3,77	0,28	0,58	1,32	1,85	4,03	0,93
14.	7,90	4,10	0,17	0,65	0,84	2,14	3,80	1,07
15.	7,10	3,65	0,19	0,73	0,82	1,71	3,45	1,05
16.	7,10	4,04	0,17	0,58	1,05	1,26	3,06	1,32
17.	7,10	3,57	0,17	0,84	1,02	1,50	3,53	1,01
18.	7,60	4,23	0,24	0,83	0,78	1,52	2,37	1,76
19.	7,40	4,23	0,14	0,65	0,79	1,59	3,17	1,32
20.	8,00	3,46	0,33	0,84	1,31	2,06	4,54	0,76
21.	8,30	5,45	0,21	0,67	0,95	1,02	4,58	1,19
22.	8,00	4,10	0,15	0,77	0,94	2,01	3,90	1,05
23.	6,40	2,63	0,33	0,69	1,40	1,35	3,77	0,69
24.	7,40	2,90	0,62	1,01	1,46	1,41	4,50	0,64
25.	6,40	2,61	0,33	0,70	1,33	1,43	3,79	0,64
26.	6,00	3,00	0,25	0,37	1,02	1,36	3,00	1,00
27.	6,80	4,05	0,20	0,56	0,88	1,11	2,75	1,47
28.	6,60	3,62	0,21	0,56	0,96	1,25	2,98	1,21
29.	7,10	3,72	0,33	0,84	1,13	1,08	3,38	1,10
30.	6,20	3,84	0,20	0,48	0,71	0,97	2,36	1,62
Mean	7,00	3,75	0,26	0,60	1,19	1,39	3,48	1,17

normal for values expressed in milligrams. In our cases, the values were low, with an average co-efficient of 16.56 in pure allergic patients and 17.98 in the infected patients.

As regards Plasma Chloride, values lower than normal were found in thirty purely allergic patients and in nine cases of infected allergic patients (81.8 per cent). Statistically this variation was also *highly significant* in both types of patients.

On the other hand, Globular Chloride was definitely increased in 90 per cent of the pure allergic cases and in 72.7 per cent of the infected allergic patients. These variations are *highly significant* in both types of patients.

The figures for total blood chloride were normal in nearly all cases.

The Globular Chloride/Plasma Chloride ratio showed an increase in globular chloride and diminution of the plasma chloride with increased averages of 0.68 in the pure allergic patients and 0.65 in infected allergic cases.

The values for calcium were within the normal limits of 9 to 11.5 mg per cent with very little difference between the purely allergic cases and the infected ones.

Magnesium also showed normal values (1.6 mg per cent to 2.9 mg per cent) although there was a slight tendency towards the lower levels. The average for the pure allergic cases was 1.97 mg per cent and 2.09 mg per cent for the infected cases.

DISCUSSION

Proteins

Examinations, both comparative and in the aggregate, made of the two classes of respiratory allergic patients studied (purely allergic patients and those with a superimposed infection) have permitted us to prove changes in the absolute quantities in some fractions of the electrophoretic register.

A most outstanding finding was the *highly significant* diminution of α_1 globulin, which can be considered as characteristic of allergic patients

TABLE IV. VALUES OF THE PLASMA PROTEINS IN INFECTED ALLERGIC PATIENTS
Given in gm. per cent

Infected Allergic Patients	Total Protein	Albumin					Total Globulin	Ind. Alb/Globulin
1.	7,60	2,97	0,32	0,79	2,20	1,32	4,63	0,62
2.	6,40	3,41	0,42	0,65	1,48	0,44	2,99	1,14
3.	6,60	3,72	0,27	0,48	0,77	1,41	3,20	1,21
4.	8,70	4,19	0,30	0,75	1,47	1,99	4,51	0,92
5.	7,60	3,42	0,30	0,69	1,46	1,73	4,18	0,81
6.	6,40	2,97	0,24	0,85	2,02	0,32	3,43	0,86
7.	7,60	3,28	0,40	0,64	1,00	1,81	4,15	0,78
8.	11,10	7,98	0,24	0,63	1,09	1,16	3,12	2,55
9.	7,60	3,88	0,33	1,00	1,11	1,28	3,82	1,01
10.	7,60	3,39	0,26	0,87	1,41	1,67	4,21	0,80
Mean	7,60	3,92	0,30	0,73	1,40	1,31	3,82	1,07

and is of definite diagnostic interest. On the other hand, no relation has been found between the intensity of the symptoms and the diminution of this fraction, which would appear to indicate a permanent modification in allergic patients. We have also performed similar investigations in allergic patients with no respiratory symptoms, for example, patients suffering from atopical eczema, and the same variations were registered.

Recent papers published by Daughday,[7,8,9] giving the results of experiments carried out with radioactive cortisone and hydrocortisone, show the carrying function of the α globulin in relation to these corticosteroids. Therefore, if we consider this fact together with the modifications observed by us in blood electrolytes, which are similar to those found in suprarenal insufficiency, we can consider the hypothesis that the low quantity of α_1 causes some difficulty in the transport of the corticosteroids, thus facilitating or conditioning the tendency of these patients to sensitivization.

As to the *significant statistical* increase of α^2 in infected allergic patients, we attribute this to the superimposed infection.

Secondly, the increase in the β globulin already pointed out by other authors in 72.5 per cent of the total patients, is also statistically *highly significant:* in the group corresponding to infected allergic patients this reached 70 per cent. The behavior of this fraction is in no way related to the increase in the gamma globulin, which would indicate that this increase is not due to a general increase in globulins as is found in chronic infections.

TABLE V. ELECTROLYTIC VALUES FOUND IN PURELY ALLERGIC PATIENTS
Given in mg. per cent

Purely Allergic Patients	Sodium	Potassium	Calcium	Magnesium	Plasma Chloride	Total Chloride	Globular Chloride	Ratio Gl. Cl/Plasma	Ratio Na/K
1.	295			2,25	332	300	259	0,78	—
2.	310	20,5	9,8	2,43	328	276	210	0,64	15,1
3.	338	21,5	11,1	2,18	360	292	208	0,58	15,7
4.	319	19,0	10,3	1,98	372	304	222	0,59	16,7
5.	328	20,7	11,2	1,95	332	280	211	0,68	15,8
6.	319	19,7	9,8	2,22	376	302	209	0,55	16,1
7.	315	19,5	10,0	1,80	334	308	270	0,80	16,1
8.					362	312	245	0,68	—
9.	323	17,5	9,8	1,40	332	280	228	0,67	18,4
10.	324	21,0	10,2	2,35	360	280	179	0,50	15,4
11.	315	19,5	10,2	1,80	334	308	270	0,80	16,1
12.	328	20,7	10,9	2,10	366	284	266	0,75	15,8
13.	331	17,0			452	372	258	0,57	19,4
14.	324	17,2	10,1	2,31	375	292	202	0,53	18,8
15.	309	20,7	10,7	2,03	344	296	248	0,69	14,9
16.	309	20,1	10,9	1,73	352	292	232	0,65	15,6
17.	334	16,9	10,9	1,98	372	280	186	0,50	19,7
18.	300	16,6			330	292	245	0,74	18,0
19.	327	16,3	10,5	2,00	356	276	196	0,54	20,0
20.	331	18,0	10,8	1,98	225	284	346	0,65	18,4
21.	330	16,1	10,8	1,63	444	368	267	0,59	20,5
22.	319	21,5	9,8	2,21	360	288	223	0,60	14,8
23.	330	19,0	10,2	1,67	360	302	217	0,60	17,6
24.	332	18,5	10,5	2,03	330	292	245	0,74	17,7
25.	312	20,1	11,3	1,93	336	292	246	0,73	15,5
26.	318	21,5	10,1	2,15	320	286	240	0,70	14,7
27.	325	18,7	9,0	2,00	366	288	170	0,46	17,7
28.	338	20,4	10,7	1,87	368	282	200	0,54	16,5
29.	318	19,2	11,0	2,20	356	296	242	0,67	16,5
30.	304	19,7	10,8	1,62	360	302	217	0,60	15,4
Mean	320	19,3	10,28	1,97	340	296	231	0,68	16,56

The increase in the β globulin is specially noteworthy as, according to Gras,[11] it is the fraction which most rarely suffers an increase; the opinions of several authors, including Cann,[3,4,5,6] who localized in this fraction the reaginic activity in the serums he examined, could explain this.

A study of the variations of the gamma globulin level shows that the amount of this is variable in purely allergic patients, with a general average of 1.39 g per cent; but on the other hand 40 per cent of high values have been found in infected patients, although we also found cases of hypogammaglobulinemia (0.32 g per cent and 0.44 g per cent) in two chronically infected asthmatic patients. This last finding could well explain the ineffectiveness of active immunization in patients who have a shortage of gamma globulins.

Again, the high gamma globulin levels could be caused by the presence of blocking antibodies in those suffering from pure allergy who have been treated by means of desensitization, according to the opinions of Cann, Loveless,[5,6] and Sehon[25] *et al* who localized the blocking antibody in the gamma fraction. In infected allergic patients, the conjunction of blocking antibodies and the antibodies produced by the superimposed infection could be the cause.

Electrolytes

The variations observed in the blood electrolytes of the patients studied, remind us of the modifications found in suprarenal insufficiency, because

there were abnormally low values in the plasma chloride (51.2 per cent of the cases studied), in the plasma Na (45 per cent) and an increase in K (34.2 per cent) (Tables III and IV). These changes are highly significant from a statistical viewpoint.

It can be said that the noticeable increase in globular chloride (an 85 per cent increase in values was found) can be due to some disturbance in acid base equilibrium which would cause a Zuntz-Hamburger phenomenon

TABLE VI. ELECTROLYTIC VALUES FOUND IN INFECTED ALLERGIC PATIENTS
Given in mg. per cent

Infected Allergic Patients	Sodium	Potassium	Calcium	Magnesium	Plasma Chloride	Total Chloride	Globular Chloride	Ratio Cl. Gl/Plasma	Ratio Na/K
1.	328	—	—	2,13	324	308	291	0,89	—
2.	319	—	—	2,10	318	288	258	0,81	—
3.	319	19,7	10,6	2,50	347	300	237	0,67	16,1
4.	301	19,0	10,0	1,50	320	286	240	0,70	15,8
5.	342	15,2	10,2	1,65	366	288	170	0,46	22,5
6.	316	19,5	10,1	1,95	285	350	158	0,45	16,2
7.	324	—	—	2,10	340	300	246	0,72	—
8.	333	18,4	9,9	1,90	340	272	170	0,50	18,9
9.	333	16,2	—	—	432	360	270	0,62	20,5
10.	331	16,6	10,2	2,10	342	274	220	0,64	19,9
11.	315	21,2	10,4	2,16	314	276	236	0,75	14,8
Mean	324	18,4	10,2	2,09	339	300	223	0,65	17,98

with the passing of the plasma chloride to the red globulins accompanied by the consequent increase in globular chloride, which can be observed in respiratory acidosis. We can, nevertheless, underestimate this mechanism, because similar abnormal values have been found in patients who at the time of examination showed no signs of respiratory insufficiency, and also in patients whose allergic manifestations were exclusively cutaneous (atopic eczema) and who had never suffered from respiratory troubles.

With our intention being to prove the possible relationship between the intensity of the symptoms and the variations in the values found, we classified the patients according to their symptoms at the time examination took place: (1) patients with no respiratory symptoms, (2) patients with some slight symptoms (hydrorrhea, nasal obstruction, sneezing, some sibilant rales), (3) patients with definite symptoms (sibilant rales, subjective dyspnea).

Similar modifications were found in all three groups of patients, the values being only slightly higher in those with definite respiratory symptoms. This slight difference could be due to a more intense allergic state of the patient concerned. The similar behavior in the three types of patients suggests a lack of any modifying influence of a possible allergic edema. On the other hand, what draws one's attention is the fact that the sodium level is found to be lower in asymptomatic patients than in those with symptoms. But, only the lowering of the plasma chloride can be attributed to a supposed respiratory acidosis, not the diminution in sodium nor the increase in K, which in this type of patient, remains the

same. Neither can the electrolytic changes in patients without any respiratory symptoms be explained by that mechanism.

The allergic patients suffering from pulmonary emphysema were studied apart, due to possible respiratory acidosis. Nevertheless, the findings in the six patients suffering from this disease showed the values to be not appreciably different from the general average.

We do not believe that these humoral modifications can be attributed to a chronic infection such as has been found by Sims, Orloff and Needham[20] in pulmonary tuberculosis. They observed a fall in Natremia difficult to explain, because it was in the allergic patients who had a superimposed infection that the electrolytic changes, although present, were in fact lower than in those suffering from allergy only. This observation leads us to a supposition that the electrolytic changes registered by us are due exclusively to allergy.

In previous papers, Rusk and his collaborators,[28] and later on Dees,[27] noticed an increase in potassium in asthmatic patients. Stoesser and Cook,[29] also considering derangements caused by a regimen rich in sodium in asthmatic patients, pointed out a link between the electrolyte balance and the mechanism of asthmatic attacks.

On the other hand, based on earlier investigations which proved (1) the excretion of the 17-ketosteroids,[10,13,15,16,26] (2) an increase in the tendency to sensitization in adrenalectomized animals,[2,18] and also (3) in the fall of the dosage of corticosteroids in the plasma of certain allergic patients,[19] we can suppose that the electrolyte changes found by us are to be attributed to a disturbance in the suprarenal function. To this disturbance should be added defective transport of the corticosteroids by the α globulin, the α_1 fraction which we found was diminished in these same patients.

SUMMARY

Using the electrophoretic paper strip technique the plasma proteins of forty allergic patients, the majority of whom were asthmatics, were studied. The patients were classified into two groups, purely allergic and allergic with superimposed infections.

The statistical diminution of α_1 fraction in both types of patients was *highly significant*. Seventy-two per cent of values inferior to normal were found.

The increase in the β fraction was also *highly significant*. Increased values in 52 per cent of the cases were proved, and this increase could be attributed to the localization of the reagins in this fraction.

Blood electrolytes were studied at the same time in the same patients. We found similar variations to those shown in suprarenal hypofunction: decrease of plasma sodium in 45 per cent of the cases; increase of potassium in 14.2 per cent of the cases; decrease of plasma chloride in 51.2 per cent of the cases. The Na/K ratio was found to be diminished as was

the case in suprarenal insufficiency, with an average coefficient in allergic patients of 16.5.

An increase in globular chloride was also substantiated in 81.3 per cent of the cases. Calcium and magnesium showed normal values in all cases.

The statistical analysis showed *highly significant* variations in the sodium, potassium and globular and plasma chloride in the purely allergic patients studied; and also *highly significant* differences in the globular and plasma chloride and *significant* differences in the sodium in the infected allergic cases.

ACKNOWLEDGMENTS

This work has been performed with patients from the Institute of Pathology and Clinical Tuberculosis under the care of Dr. Raul F. Vaccarezza and with private patients of Prof. Guido Ruiz Morenco. This analyses were performed in the Central Laboratory of the Muñiz Hospital under the care of Prof. Américo J. Vaccarezza. The statistical analyses were performed in collaboration with Dr. Juan H. Tramezzani. To all who made this study possible, we extend our thanks.

BIBLIOGRAPHY

1. Andersson, E.: Adrenal cortical function in bronchial asthma and its diagnostic value. Acta Allergol, 6:107, 1953.
2. Banting, F. G., and Gairns, S.: Suprarenal insufficiency. Am. J. Physiol., 77:100, 1926.
3. Cann, J. R., Brown, H. A., Gaidusek, D. C., Kirkwood, J. G., and Sturgeon, P.: Fractionation of RH anti-serum by electrophoresis convection. J. Immunol., 66:137, 1955.
4. Cann, J. R., Brown, R. A., Kirkwood, J. G., Sturgeon, D., and Clarke, D. W.: J. Immunol., 68:243, 1952.
5. Cann, J. R., and Loveless, M. H.: Distribution of sensitizing antibody in human serum proteins fractionated by electrophoresis convection. J. Immunol., 72:270, 1954.
6. Cann, J. R., and Loveless, M. H.: Biophysical characterization of Reaginic and blocking sera. J. Allergy, 28:379, 1957.
7. Daughday, W. H.: Binding of corticosteroids by plasma protein. J. Clin. Invest., 35:1434, 1956.
8. Daughday, W. H.: Corticosteroids binding by plasma alpha globulin. J. Clin. Invest., 36:881, 1957.
9. Daughday, W. H.: Binding of corticosteroids by plasma protein. A. M. A. Arch. Inter. Med., 101:286, 1958.
10. Ericksson-Lihr, Z., Forsell, P., Pettay, O., and Ruski, I.: Investigation of the function of suprarenal cortex allergic diseases. Acta Allergol, 2:249, 1949.
11. Gras, J.: Proteinas plasmáticas. Edit. Jims. Barcelona, 1956.
12. Hioco, D., and Santer, M.: Descretion of 17-ketosteroids 11-oxycorticosteroid and 11-desozycorticosteroid in patients with bronchial asthma. J. Clin. Endocrinol., 10:1570, 1950.
13. Knapp, P.H., and Michelson, A.: Psychiatric-pulmonary and adrenocortical observation in bronchial asthma. J. Allergy, 26:80, 1955.
14. Kuhns, W. J.: Immuno chemical studies of antitoxin produced in normal and allergic individuals hypersensitized with diphtheria toxoid. J. Exper. Med., 100:485, 1954.
15. Rackemann, F. M.: Depletion in asthma. J. Allergy, 16:136,1945.
16. Rose, B., Ffyles, T. W., and Verning, E. H.: Corticotropin cortisone and Hydrocortisone in diseases of hypersensitivity. J. Allergy, 26:1, 1955.
17. Scott, W. J. M.: The influence of the adrenal gland on resistance susceptibility to histamine as a test of adrenal deficiency. J. Exper. Med., 47:185, 1928.
18. Selye, H.: Studies on adaptation. Endocrinology, 21:169, 1937.
19. Siegel, S., Ely, R. S., Bernberg, V., and Kelley, V. C.: Adrenal function in allergy. J. Allergy, 6:504, 1956.

20. Sims, E. A. H., Woet, L. G., Orloff, I., and Needhan, J. W.: Asymptomatic hiponatremia in pulmonary tuberculosis. J. Clin. Invest., 29:950, 1950.
21. Fawcett, J. K., and Wynn, V.: Variation of plasma electrolyte and total protein levels in the individuals. Brit. M. J., 4992:582, 1956.
22. Vaccarezza, J. R., Bonacossa Torrent, R. J., and Willson, J. A.: Estudio de las proteinas plasmáticas en los alérgicos respiratorios. An. Cat. Pat. Clin. de la Tuberc., 16:86, 1957.
23. Vaccarezza, J. R., Bonacossa Torrent, R. J., and Willson, J. A.: Estido de los electrolitos sanquineos en los alérgicos respiratorios. An. Cat. Pat. Clin. de la Tuberc., 16:66, 1957.
24. Houssay, B., Lewis, J. T., Orias, O., Braun Menendez, E., Hug, E., and Foglia, V.: Fisiología Humana., Edit. Ateneo Buenos Aires. 1957.
25. Sehon, A. H., Hollinger, H. Z., Naster, J. G., Schweitzer, A. E., and Rose, B.: Localization of blocking antibody in sera of ragweed-sensitive individuals by starch electrophoresis. J. Allergy, 3:229, 1957.
26. Israel, E. E., Dingemanse, E., Ruis Veld, L. G., and Orie, N. G. M.: Discretion of neutral 17-ketosteroids of adrenal and gonadal origin in bronchial asthma with and without a bacterial bronchitis. Acta Allergol., 16:55, 1953.
27. Dees, S. C.: Ann. Allergy, 3:64, 1945.
28. Rusk, H. A.: Weichselbaum, T. E., and Somogyi, M.: Changes in serum potassium in certain allergic states. J.A.M.A., 112:1395, 1939.
29. Stoesser, A. V., and Cook, M. M.: Possible relationship between electrolyte balance and bronchial asthma. Am. J. Dis. Child., 56:943, 1938.
30. Stoesser, A. V., and Cook, M. M.: Electrolyte and water exchange in bronchial asthma. J. Allergy, 11:65, 1940.

Paraná 981

SCIENTISTS—A UNIQUE FRATERNITY

Scientists constitute a fraternity which is unique and which is collectivistic, though not in the sense that adherents of Stalin use the term. How many first-class research physicists, biologists, chemists, and engineers there are in the world no one knows. The number cannot be far from two hundred fifty thousand. In other words, two hundred fifty thousand men and women, varying widely in religious creed, political conviction, color, and nationality, all of outstanding intellectual power, have tried to sink prejudices, patriotism, differences in personal belief, in a common cause. These men and women in normal times meet in international conventions and give freely of their knowledge. There is no spectacle quite like this. Idealists may preach on the brotherhood of man. Science does its best to convert sermons into realities.—WALDEMAR KAEMPFFERT—From *Explorations in Science,* the Viking Press, New York, 1953.

THE EFFECT OF ESTRUS ON THE RESPONSE OF THE EXCISED MOUSE UTERUS TO SEROTONIN, ACETYLCHOLINE, AND SPECIFIC ANTIGEN

Schultz-Dale Tests with the Physiograph

KENNETH L. BURDON, Ph.D., F.Sc.A.C.A., KEMAL OZKARAGOZ, M.D., HERBERT S. KAUFMAN, B.A., and JOHN P. McGOVERN, M.D., F.A.C.A.

Houston, Texas

SINCE the second decade of this century, the Schultz-Dale technique[1,2] has been widely employed to study the effects of various cholinergic compounds upon the normal excised uterine or intestinal tissue, and to observe the reactions of sensitized smooth muscle challenged by specific antigens. Details of the method have been significantly improved in recent years, but nearly all investigators have followed the original basic procedures for recording the muscle contractions. These involve use of a kymograph and muscle lever, with tracings on a drum of smoked paper.[3-5] Katsh and Marshall[6] have supplemented these usual records with measurements of electrical responses detected by inserting electrodes into the smooth muscle tissue.

In the present study advantage has been taken of the availability of the electronic recorder developed by Hoff, Geddes and Spencer[7,8] in the Department of Physiology of the Baylor University College of Medicine, called the Physiograph* (Fig. 1). This sensitive instrument permits recording of the responses of smooth muscle strips from the uterus or the ileum with great accuracy and convenience. The contractile responses of two separate pieces of smooth muscle may be recorded simultaneously on the same sheet of graph paper. The speed of movement of the paper may be regulated at will in conformity with a timer, and a continuous record may be made over a period of hours. A feature of special importance is an adjustable amplifier which allows for precise calibration of the instrument before beginning experiments. During a series of tests the physiological state of the smooth muscle tissue in use is continuously evident, and its responsiveness to a known stimulus can be checked quantitatively at any time under strictly controlled, uniform conditions. Thus, with the physiograph a quantitative evaluation can be made of all results.

It is well known that the uterus responds actively to estrogens, and that in rats the estrous uterus exhibits increased contractility.[9-11] A significant effect of estrus in the rat upon responses to serotonin was mentioned by Erspamer[12] and studied in more detail by Robson *et al*[13] in 1954. These authors found

---

From the Department of Microbiology, Baylor University College of Medicine, Houston, Texas.

Supported by Research Grant E-1563 and Training Grant 2E-47, National Institute of Allergy and Infectious Disease, USPHS.

Dr. Ozkaragoz is a Fellow in Pediatric Allergy at Baylor University, and Mr. Kaufman is a student trainee in Allergy and Immunology at Baylor University.

*E & M Instrument Co., Inc., P.O. Box 14013, Houston 21, Texas.

that the diestrous rat uterus was relatively insensitive to serotonin, whereas in estrus, induced by injection of stilbestrol or estradiol, the uterine tissue became highly sensitive.

Fink and Rothlauf[14] in the only previous study of which we are aware on Schultz-Dale reactions of the uteri of sensitized mice, injected their animals

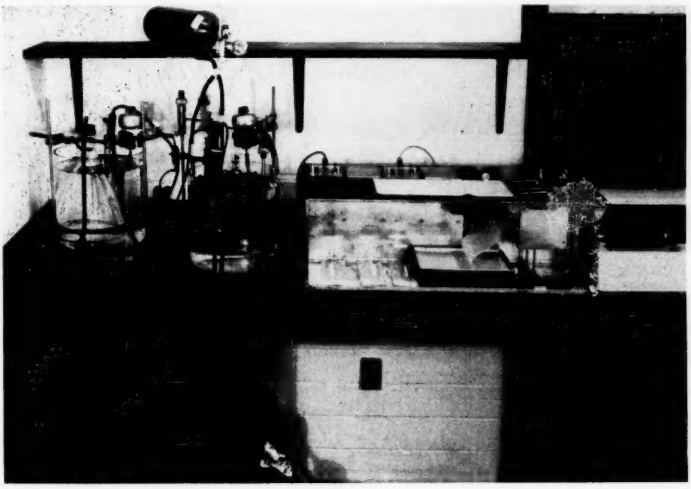


Fig. 1. The Physiograph and accessories arranged for the tests described. The water bath at the left contains the reservoir of Tyrode's solution maintained at 37°C. The bath at the right contains the two separate chambers, each containing 10 ml of Tyrode's solution, in which the uterine strips are placed. The rubber tubes provide for oxygenating and for flushing out the tissue baths. Each tissue strip is attached to a separate myograph transducer; the impulse resulting from contractions of the muscle passes through an amplifier and then activates the connected recording needle.

with an estrogen four to five days before excising the uterine tissue. A search of the literature has revealed no publications to date in which systematic quantitative observations have been made of the effect of the natural estrous state in the mouse upon the results of Schultz-Dale tests.

The studies reported here were designed to investigate the effect of estrus upon the reactivity of normal mouse uteri to serotonin (5-hydroxytryptamine), and to acetylcholine, as compared to the responses of sensitized mouse uteri to these same chemicals, and to the specific antigen. Serotonin rather than histamine, was chosen as one of the test reagents because of the relatively high sensitivity of the uterine tissue of mice and of rats to this compound, and its probable importance in anaphylactic reactions in these species.[15,16]

MATERIALS AND METHODS

Tyrode's Solution, pH 7.5.—This solution was made fresh for each day's experiments. For the earlier tests (Experiment I), it was prepared to contain

in one liter of deionized distilled water: NaCl, 8 g, $CaCl_2$, 0.25 g, KCl 0.2 g, $NaHCO_3$, 0.5 g, $MgCl_2$, 0.2 g, $NaHPO_4$, 0.000375 g, glucose, 0.5 g. For convenience and accuracy in weighing, the solution was customarily prepared in 6 to 10 liter amounts. For Experiment II the amount of $CaCl_2$ was reduced to 0.05 g per liter, as recommended by Coulson.[3] This had the effect of reducing markedly the spontaneous contractions of the uterine strips, which were often of considerable magnitude in standard Tyrode's solution. At the same time the degree of contraction following a known stimulus (for example by 10γ acetylcholine) remained at the same amplitude.

Serotonin.—A stock solution of serotonin creatinine sulfate (obtained from the Nutritional Biochemical Corporation, Cleveland, Ohio) was prepared by dissolving 57.58 mg (equivalent to 25 mg serotonin base) in 100 ml of Tyrode's solution. This was stored at 4°C. Immediately before use in the tests 1.0 ml of this stock solution was diluted to 100 ml with Tyrode's solution to give a concentration of 2.5γ serotonin base per ml.

Acetylcholine.—A stock solution of acetylcholine chloride (Merck) was made by dissolving 124.28 mg (equivalent to 100 mg acetylcholine base) in 100 ml Tyrode's solution. It was kept at 4°C. One milliliter of this stock solution was diluted to 100 ml with Tyrode's solution to make a concentration of 10γ of acetylcholine base per ml immediately before the tests.

Active Sensitization of Mice.—Seventy-five mice were sensitized actively by two subcutaneous injections, at an interval of five days, of Armour's crystalline egg albumin antigen (CEA), plus Bacto adjuvant complete, Freund (Difco). Each dose contained 0.75 mg CEA. Twenty-one days after the last sensitizing injection, a group of mice in estrus, and others not in estrus, were selected and challenged by intravenous injection of the antigen. Typical anaphylactic reactions were observed, including fatal shock, accompanied by the expected drop in rectal temperature.[17] Non-sensitized control animals did not show any signs of illness after similar antigen injections.

Selection and Preparation of Mouse Uterine Horns.—Female Swiss mice, four to six weeks old, weighing 20-30 gms, were used. No estrus-inducing drugs were administered. To detect the occurrence of the natural estrous state, vaginal swabs were made at frequent intervals and smeared on clean glass slides and allowed to dry. These were examined without staining by the method recommended by Allen.[18] The four recognized stages in the menstrual cycle, namely proestrus, estrus, metestrus and diestrus, were readily identified by this procedure. In presenting the results of our experiments, however, we have divided the animals into just two groups: (1) those in estrus and (2) those not in estrus.

Animals selected for the Schultz-Dale tests after examination of vaginal

smears, were sacrificed by decapitation. The uterus was removed by abdominal incision. The broad ligament was trimmed from the uterine horns and the halves were separated by mid-section of the cervix.

Operation of the Physiograph.—Before beginning each experiment the instrument was calibrated so that the weight of a particular metal mass (0.6869 g) would cause a deflection of the recording needles of exactly 30 mm (Fig. 1, C). The two-channel physiograph was arranged to record simultaneously changes in the contraction of smooth muscle tissue strips in

TABLE I. RESPONSE OF UTERI FROM NORMAL MICE

Experimental Animals			Tested Material	Response (Muscle Contraction): Deflection of Recording Pen in mm				
Number of Mice	Uterus Horns	Condition		0	0-10	10-25	25-40	40-70
30	60	Not in estrus	S	15	35	10	—	—
			Ach	19	38	3	—	—
20	40	In estrus	S	—	—	3	12	25
			Ach	—	—	4	12	24

Ach=Acetylcholine (10γ in 10 ml. tissue bath).
S=Serotonin (2.5γ in 10 ml. tissue bath).

two separate baths, each having a volume of 10 ml. The muscle was attached to the myograph transducer with #40 cotton thread. The temperature of the baths was maintained at 37°C(±1°) and they were continuously oxygenated with a mixture of 95 per cent oxygen and 5 per cent carbon dioxide.

TABLE II. RESPONSE OF UTERI FROM SENSITIZED MICE

Experimental Animals			Tested Material	Response (Muscle Contraction): Deflection of Recording Pen in mm				
Number of Mice	Uterus Horns	Condition		0	0-10	10-25	25-40	40-70
24	48	Not in estrus	S	3	32	13	—	—
			Ach	2	38	8	—	—
			CEA	13	23	12	—	—
20	40	In estrus	S	—	—	—	6	34
			Ach	—	—	—	5	35
			CEA	—	—	—	4	36

Ach=Acetylcholine (10γ in 10 ml. tissue bath).
S=Serotonin (2.5γ in 10 ml. tissue bath).
CEA=Crystalline egg albumin antigen (300γ in 10 ml. tissue bath).

EXPERIMENT I

Response of Uteri from Normal Mice

Procedure.—Fifty mice were included in this experiment; thirty of them were not in estrus and twenty were in estrus. The two horns of the uterus from the same mouse were suspended in two separate baths, and allowed to attain an equilibrium, as indicated by a stable base line recording. One ml (10γ) of the acetylcholine test solution was then added to one of the baths, and one ml (2.5γ) of the serotonin test solution was introduced into the

TABLE III. SUMMARY: EFFECT OF ESTRUS ON RESPONSE OF MOUSE UTERI IN SCHULTZ-DALE TESTS

Animals	Number of Uterine Horns Tested	Test Reagents					
		Serotonin (0.25γ/ml.)		Acetylcholine (1.0γ/ml.)		Specific Antigen (30γ/ml.)	
		Positive Responses	Average Contraction	Positive Responses	Average Contraction	Positive Responses	Average Contraction
Normal mice							
Not in estrus	60	75%	7.9 mm.	68.3%	5.9 mm.		
In estrus	40	100%	57.2 mm.	100%	44.5 mm.		
Sensitized mice							
Not in estrus	48	94%	8.4 mm.	95.8%	7.2 mm.	73%	9.3 mm.
In estrus	40	100%	51.4 mm.	100%	48.1 mm.	100%	52.7 mm.

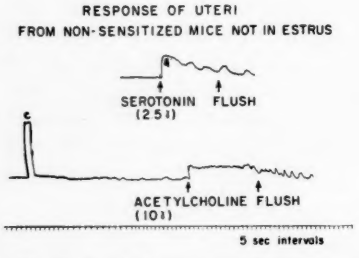


Fig. 2. Typical responses of the uterine tissue of normal (non-sensitized) mice not in estrus. C=calibration: 30 mm deflection produced by a standard weight.

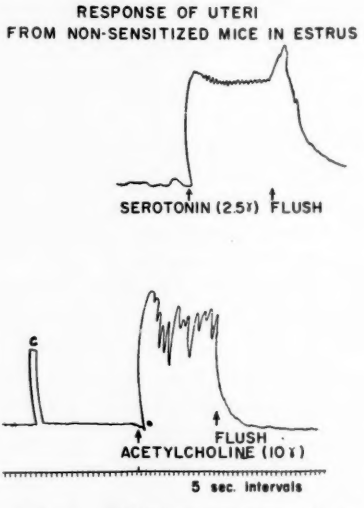


Fig. 3. Typical contractions of the uterine muscles of normal (non-sensitized) mice in estrus. Compare with Figure 2. C=calibration: 30 mm deflection produced by a standard weight.

other bath. The response of the muscle, if any, was always immediate. If no contraction occurred at once, a period of a few minutes was allowed to elapse before flushing out these test solutions and continuing the experiment. The tissue first tested with acetylcholine was now tested with serotonin, and the other with acetylcholine. The order in which the reagents were added had no discernible effect upon the magnitude of the responses obtained.

The baths were thoroughly cleaned and the physiograph recalibrated before repeating these tests with uterine horns from other animals.

Results.—The responses obtained in the experiments above described are summarized in Tables I and III.

Of the sixty uterine horns from the thirty normal mice *not in estrus,* fifteen (25 per cent) did not respond to serotonin, and nineteen (32 per cent) failed to react to acetylcholine. The majority of the uteri gave only a slight response to these reagents, representing a needle deflection of not more than 10 mm, and averaging 7.9 mm for serotonin and 5.9 mm for acetylcholine.

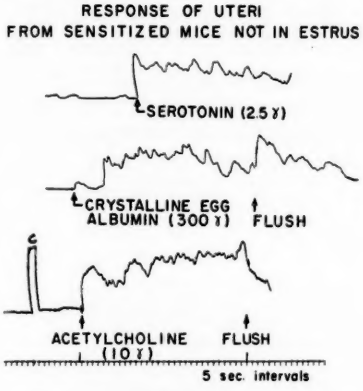


Fig. 4. Recorded responses of uteri from sensitized mice not in estrus. Note that these reactions to the standard amounts of serotonin and of acetylcholine are somewhat greater than those shown by the non-sensitized, non-estrous mice (Fig. 2). C=calibration: 30 mm deflection produced by a standard weight.

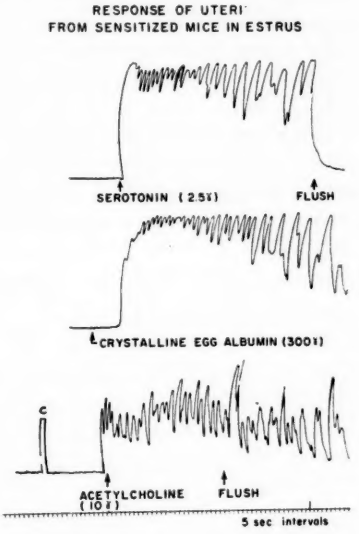


Fig. 5. Typical responses of uterine strips from sensitized mice in estrus. Compare with Figure 4. C=calibration: 30 mm deflection produced by a standard weight.

In contrast the forty uterine horns from twenty normal mice *in estrus* responded very much more actively. The reaction to acetylcholine and serotonin was essentionally equal; all the uterine horns contracted, the majority deflecting the recording pens 40 to 70 mm. Averages of 57.2 mm and 44.5 mm were recorded for serotonin and acetylcholine respectively.

The markedly greater sensitivity to serotonin and to acetylcholine of the uterine tissue from normal mice *in estrus* is demonstrated in Figures 2 and 3.

EXPERIMENT II

Response of Uteri from Sensitized Mice

The two uterine horns from each of twenty-four sensitized mice not in estrus were separately tested, as in Experiment I, for sensitivity to serotonin and to acetylcholine. Similarly, the two uterine strips from each of twenty sensitized mice in estrus were tested with the same reagents. Each of the tissue pieces was then brought in contact with the specific sensitizing antigen by adding 300γ CEA to the baths.

Results.—The findings are summarized in Tables II and III, and demonstrated in Figures 4 and 5. With the uteri from the sensitized mice *not in estrus* the responses to serotonin were similar in magnitude (about 8 mm) to those observed with the nonestrous normal mice in Experiment I, but a greater percentage (94 per cent) of the tissue strips reacted. Acetylcholine caused contractions in forty-six (96 per cent) of the tested uterine horns from those sensitized mice not in estrus, and the average needle deflection was 7.2 mm. Following addition of the specific antigen thirty-five (73 per cent) of the uteri responded, but the contractions were slight, averaging only 9.3 mm.

The parallel tests with uterine horns from sensitized mice *in estrus* again showed a strikingly greater activity. One hundred per cent of the tissue strips contracted strongly when the test amount of serotonin or of acetylcholine was added to the bath, and the average needle deflections were 48-51 mm. All of the uteri responded vigorously also to contact with the specific antigen, with an average excursion of about 53 mm.

DISCUSSION

In these experiments, it has been possible to make a valid comparison of the relative degree of contractile response to be expected when excised uteri from mice in estrus and from mice not in estrus are subjected to a comparable stimulus. By the use of the physiograph, which permits standardization and continuous control of all conditions of the tests, the first responses of the tissue strips may be compared directly in terms of the height, in millimeters, of the excursions made by the recording needles. Using this measurement, the estrous mouse uterus was found to respond, on the average, with contractions about seven times as great as those of the non-estrous uterus. This effect of the estrous state was essentially the same when the test reagent was serotonin, or acetylcholine alone, or in the case of the sensitized mice, the specific antigen.

The uteri removed from mice in the estrous state were obviously increased in weight and size over those excised in diestrus, or at intermediate stages of the menstrual cycle. A considerable variation in the contractile response of uterine tissues from different mice classified as "not in estrus" was observed, while the contractions of the different mice in estrus were more nearly constant. (Tables I and II). This may be due to the fact that we did not attempt to subdivide the former group according to intermediate stages of the estrus cycle.

It is evident that critical studies of Schultz-Dale reactions with mouse uteri must take into account the marked effect of the estrous state upon the contractility of the uterine tissue. It seems likely that tests using intestinal smooth muscle might be affected also.

Studies of the type described here might be appropriately extended to other species, with additional reagents, and with the use of ileum as well as uterus.

SUMMARY

The excised uterine tissues from mice in estrus were shown to be significantly more sensitive to small amounts of serotonin and of acetylcholine in Schultz-Dale tests than the uteri from mice not in estrus. Also, the uterine horns from actively sensitized mice in estrus displayed a greater contractility on contact with the specific antigen than did those from similarly sensitized mice not in estrus. The increase in the amount of contraction to the same stimuli in the estrous state over the non-estrous state was about seven-fold.

These comparisons between the relative sensitivity of uterine issues from estrous and non-estrous mice were made under the strictly controlled conditions afforded by use of the physiograph, a sensitive electronic recorder, which permits a valid quantitative evaluation of results.

Future critical investigations using mouse uteri in Schultz-Dale tests must take into account the significant effect of the estrous state upon the contractility of the uterine tissue.

ACKNOWLEDGMENT

The authors wish to acknowledge the valuable suggestions made at the beginning of the work by Dr. Wayne M. Meyers.

REFERENCES

1. Schultz, W. H.: Physiological studies in anaphylaxis. 1. The reaction of smooth muscle of the guinea pig sensitized with horse serum. J. Pharmacol. & Exper. Therap., 1:549, 1910.
2. Dale, H. H.: The anaphylactic reaction of plain muscle in the guinea pig. J. Pharmacol. & Exper. Therap., 4:167, 1913.
3. Coulson, E. J.: The Schultz-Dale Technique. J. Allergy, 24:458, 1953.
4. Geiger, W. B., and Alpers, H. S.: The mechanism of the Schultz-Dale reaction. J. Allergy, 30:316, 1959.
5. Katsh, S.: Demonstration in vitro of anaphylactoid response of the uterus and ileum of guinea pigs injected with testis or sperm. J. Exper. Med., 107:95, 1958.
6. Katsh, S., and Marshall, J. M.: Electrical and mechanical responses of uterine smooth muscle during anaphylaxis in vitro. Amer. J. Physiol., 196:39, 1959.
7. Hoff, H. E., Geddes, L. A., and Spencer, W. A.: The Physiograph—an instrument for teaching physiology. J. Med. Education, 32:181, 1957.
8. Hoff, H. E., Geddes, L. A., and Spencer, W. A.: Instrumentation in medical education. Instruments & Automation, 30:1712, 1957.
9. Corner, G. W., and Csape, A.: Action of the ovarian hormones on uterine muscle. Brit. M. J., 1:687, 1953.
10. Reynolds, S. R. M.: The nature of uterine contractility, a survey of recent trends. Physiol. Rev., 17:304, 1937.
11. Velardo, J. T., Editor: The endocrinology of reproduction. New York: Oxford University Press, 1958.
12. Erspamer, V.: Observations of alleged serotonin (enteromine)—like nature of cerebral pressor substance of Taylor, Page and Coccoran. A.M.A. Arch. Int. Med., 90:505, 1952.
13. Robson, J. M., Trounce, J. R., and Didcock, K. A. H.: Factors affecting the response of the uterus to serotonin. J. Endocrin., 10:129, 1954.
14. Fink, M. A., and Rothlauf, M. V.: *In vitro* anaphylaxis in the sensitized mouse uterus. Proc. Exper. Biol. & Med., 90:477, 1955.
15. Page, J. H.: Serotonin (5-hydroxytryptamine); the last four years. Physiol. Reviews, 38:277, 1958.
16. Fink, M. A.: Anaphylaxis in the mouse: Possible relation of the Schultz-Dale reaction to serotonin release. Proc. Soc. Exper. Biol. & Med., 92:673, 1956.
17. Meyers, W. M., and Burdon, K. L.: Inhibition of anaphylaxis in mice by pretreatment with cysteine, lysine ethyl ester, and tyrosine ethyl ester. Experientia, 16:52, 1960.
18. Allen, E.: The oestrous cycle in the mouse. Am. J. Anat., 30:297,1922.

AN INVESTIGATION INTO THE USE OF ARALEN IN BRONCHIAL ASTHMA

ARTHUR STERN, M.D., ALBERT ZUCKER, M.D., F.A.C.A., WILLIAM SHERMAN, M.D., and ALDO FLORIO, M.D., F.A.C.A.

New York, New York

THE VALUE of antimalarial agents in some of the collagen diseases has been demonstrated since Page's first article in 1951 on the use of quinacrine in lupus erythematosus.[1] Since then a variety of other antimalarials have been shown to be of value in such conditions as rheumatoid arthritis,[2] scleroderma[3] and solar dermatitis.[4] Although the exact mechanism of action of the antimalarial drug is not known, several hypotheses have been advanced, such as the hyaluronidase inhibiting effect[5] and the alteration of adenosine triphosphate in the tissues.[6] The anti-inflammatory effect of the antimalarials is not steroidal and there is no stimulation of the adrenal cortex.[7]

It was felt that, inasmuch as the collagen diseases were favorably affected by the antimalarial drugs, it would be worthwhile to determine their value in bronchial asthma, especially in view of the fact that the drugs have been shown to be concentrated in nucleated cells of the lung as well as the liver, the spleen and the kidney.[8]

MATERIALS AND METHODS

For the purpose of this study Aralen Phosphate,® a brand of chloraquine manufactured by the Winthrop Laboratories, was employed. It was after the study began that it was given added impetus by the abstract of an article by A. Engeset[9] which appeared in the *Journal of the American Medical Association*. The author claimed various degrees of improvement in 75 per cent and marked improvement in 53 per cent of thirty-two asthmatic patients.

The study was controlled by the double-blind method: the active drug in 0.25 gm tablets and placebo, both furnished by the Winthrop Laboratories, were identical in size, shape, and appearance. They were dispensed in such a manner that none of the participants (patient, physician or nurse) knew whether any given patient was receiving the active drug or the placebo. All other medication and/or treatment were suspended for the duration of the study. Alternate patients, previously untreated or treated only symptomatically, were given the drug or placebo without regard to the nature or severity of the asthma. The dosage for all patients was 0.25 gm daily. Clinical impression, blood studies, x-rays and timed vital capacities were recorded before and after treatment.

From the Allergy Clinic of the Harlem Hospital, New York City Department of Hospitals.

TABLE I.

Case	Age	Sex	Severity of Asthma Before, After Treatment		Positive Skin Tests	Medication		Pulmonary Function		Changes
						Type	Durat.	Before	After	
1.	65	F	Mod. sev.	Sl. Impr.	H. dust	AR	6 mos.	87%	85%	−2%
2.	23	F	Mod. sev.	No change	M. grasses H. dust	AR	9 wks.	100%	96%	−4%
3.	49	F	Mod. sev.	No change	H. dust	AR	1 yr.	79%	89%	+10%
4.	28	M	Mod. sev.	No change	H. dust Foods	AR	1 yr.	100%	100%	0
5.	47	F	Severe	No change	Ragweed Molds	AR	1 yr.	95%	100%	+5%
6.	59	F	Mod. sev.	No change	Neg.	AR	6 mos.	80%	86%	+6%
7.	51	F	Mod. sev.	No change	Neg.	AR	11 mos.	85%	87%	+2%
8.	49	M	Severe	No change	H. dust	AR	6 mos.	81%	82%	+1%
9.	53	M	Mod. sev.	No change	H. dust	AR	4 mos.	68%	94%	+26%
10.	25	M	Severe	Mkd. impr.	H. dust Ragweed M. grasses	PL	6 mos.	90%	85%	−5%
11.	19	M	Mod. sev.	Sl. impr.	H. dust Ragweed Feathers Foods	PL	6 mos.	86%	85%	−1%
12.	19	M	Severe	Mkd. impr.	H. dust Foods Ragweed M. grasses	PL	4 mos.	100%	100%	0
13.	13	M	Mod. sev.	Mkd. impr.	H. dust Ragweed	PL	5 mos.	100%	100%	0
14.	54	F	Severe	No change	H. dust	AR PL	4 mos.	74%	73%	−1%
15.	48	F	Severe	No change	Neg.	AR PL	6 mos.	74%	76%	+2%
16.	37	F	Mod. sev.	Mkd. impr.	Neg.	AR PL	2 mos.	84%	82%	−2%

AR—Aralen PL—Placebo.

Above pulmonary function studies were done with Gaensler-Collins Timed Vitalometer and represent three seconds vital capacity as expressed in percentage of patient's total vital capacity.

RESULTS

The study was initiated with twenty-five patients. Of this number, nine have not been included in our final tabulation because they either discontinued therapy completely on their own initiative or had extremely poor attendance. At the conclusion of the study it was found that of the remaining sixteen patients, nine had received Aralen, four the placebo and three both Aralen and placebo because they had shown adverse effects: patient No. 14 stated that Aralen caused nausea and vomiting, patient No. 15 was changed from Aralen to placebo because of the severity of the asthma and patient No. 16 was changed from placebo to Aralen because of nausea and vomiting.

X-ray studies of the above patients failed to show any abnormalities of the lungs. After treatment, no significant changes were noted in white cell, differential or circulating eosinophile counts. Of the nine patients on Aralen, six showed an increase in timed vital capacity, one showed no change and two a diminution. Of the four controls, two showed a diminution in timed vital capacity and two showed no change. Clinical evaluation was based on the patient's subjective complaints and periodic chest examinations. Of the nine patients on Aralen, the results in eight were considered poor and in one fair. Of the four patients who were given the placebo, three were markedly improved and one slightly improved.

COMMENT

The results of our study indicate that there are no beneficial effects from the use of Aralen in the treatment of long-standing bronchial asthma. This does not support the findings of Engeset in the article mentioned above. The dosage schedule employed by the latter differed slightly from ours—his patients received 0.25 gm twice daily for one week, then 0.25 gm once a day subsequently. We do not feel, however, that this could account for the difference in results.

There were no serious toxic effects observed—one patient on Aralen complained of nausea which promptly subsided upon discontinuance of the drug. It will be noted from the table that the pulmonary function showed improvement in the patients who received the Aralen. This improvement could not be correlated with clinical results.

SUMMARY

Sixteen patients participated in a double-blind evaluation of Aralen in the treatment of bronchial asthma. Although pulmonary function was improved in patients taking the drug, there was no apparent clinical improvement with the dosage employed in our study.

ACKNOWLEDGMENT

The authors wish to express their gratitude to J. Rice and E. Mylod of Winthrop Laboratories for the supply of Aralen and the donation of a spirometer for the pulmonary function studies.

REFERENCES

1. Page, F.: Treatment of lupus erythematosus with Mecaprine. Lancet, 2:755-758 (Oct. 27, 1951.
2. Haydu, G. G.: Rheumatoid arthritis therapy; a rationale and the use of chloraquine. Am. J. M. Sc., 225:71 (Feb.) 1953.
3. Winkelman, R. K., and Brunsting, L. A.: The treatment of scleroderma. Minnesota Med., 42:13 (Jan.) 1959.
4. Knox, J. M. et al: Light sensitive eruptions treated with atabrine and chloraquine. J. Invest. Dermat., 22:11 (Jan.) 1954.
5. Rinehart, R. E.: Chloraquine therapy in rheumatoid arthritis. Northwest Med., 56:703 (June) 1957.
6. Goodman, L. S., and Gilman, A.: The Pharmacological Basis of Therapeutics. p. 1167, New York: The Macmillan Co., 1955.
7. Shelly, W. B., and Arthur, R. P.: The failure of chloraquine to stimulate the human adrenal cortex. J. Invest. Dermat., 31:109 (Aug.) 1958.
8. Loeb, R. F. et al: Activity of a new antimalarial agent, chloraquine. J.A.M.A., 130:1069 (Apr. 20) 1946.
9. Engeset, A.: Therapeutic experiments with antimalarials in the treatment of bronchial asthma. Nord. Med., 58:1904 (Dec. 5) 1957.

160 West 73rd Street (Dr. Arthur Stern)

THE IDEAL SCIENTIST

The bloodless, unemotional "ideal" scientist of the novelists would have no morals, no scruples, no patriotism, no love or hate. He would slit the throat of his grandmother if he thought that only thus could he discover a new and important scientific fact. Fortunately there is no ideal scientist.—WALDEMAR KAEMPFFERT—From *Explorations in Science*, the Viking Press. New York, 1953.

STUDIES OF THE DISPERSION OF EMULSIFIED EXTRACTS BY MEANS OF INCORPORATED RADIOISOTOPES

T. G. METCALF, Ph.D., A. R. AMELL, Ph.D., and L. W. SLANETZ, Ph.D.
Durham, New Hampshire

ETHAN ALLAN BROWN, M.R.C.S. (England); L.R.C.P. (London), F.A.C.A.
Boston, Massachusetts

IN A PREVIOUS study[1] we reported that the greater portion of a water-in-mineral oil type of emulsion in guinea pigs was, at the end of five days, noted as being retained at the original point of deposition. Some of the emulsion, however, spread from the point of injection through the adjacent tissues. The present study was initiated to study the rate of such a spread of a Drakeol 6VR-Arlacel A type of emulsion from a subcutaneous point of deposition and if possible, to follow its course of dissemination through the body of the test animal.

MATERIALS AND METHODS

Sodium radio-iodide (Iodotope therapeutic capsules, E. R. Squibb & Sons representing 5 millicuries of I^{131}) was used to iodinate bovine gamma globulin (Nutritional Biochemicals Company). The sodium iodide was carrier-free.

Of a 0.1 N solution of inactive potassium iodide, 0.2 ml was added to 10 ml of distilled water. The iodide was oxidized with excess nitrous acid (equal volumes of 0.1 N HCL and $NaNO_2$), and the resulting iodine extracted with 10 ml of carbon tetrachloride. The iodine was then extracted from the carbon tetrachloride by 10 ml of 0.1 N sodium hydroxide solution. The capsule of radio-iodide was added to this solution and allowed to dissolve. Of a 5 per cent solution of bovine gamma globulin (BGG), in a phosphate buffer, pH 7.0, 10 ml was added and then 1 ml of a pH 7 phosphate buffer containing .01 ml of a 1.33 M solution of potassium iodide, saturated with iodine. This mixture stood overnight. To remove the non-protein bound iodine, the solution was dialyzed against a 1 per cent sodium chloride solution. The dialysis was continued until the sodium chloride solution gave no indication of iodine activity as determined by means of a well-type scintillation counter. (Nuclear-Chicago Model DS 5-5 connected to a Nuclear-Chicago Model 181-A Scalar). The iodine content of the resulting BGG solution was calculated as 2 atoms of Iodine for each molecule of BGG. The activity was so great that the scintillation counter jammed when attempts were made to do counts on a 0.1 ml portion.

Dr. Metcalf is in the Department of Bacteriology; Dr. Amell, in the Department of Chemistry; Dr. Slanetz, in the Department of Bacteriology, University of New Hampshire, Durham, New Hampshire.
Dr. Brown is Director, Asthma Research Foundation, Boston, Massachusetts.

The tagged antigen was mixed with equal volumes of the saline solution and a sterile Arlacel A:Drakeol 6VR (1:9) mixture. The ingredients were then emulsified by means of a Brown Emulsor.[2]

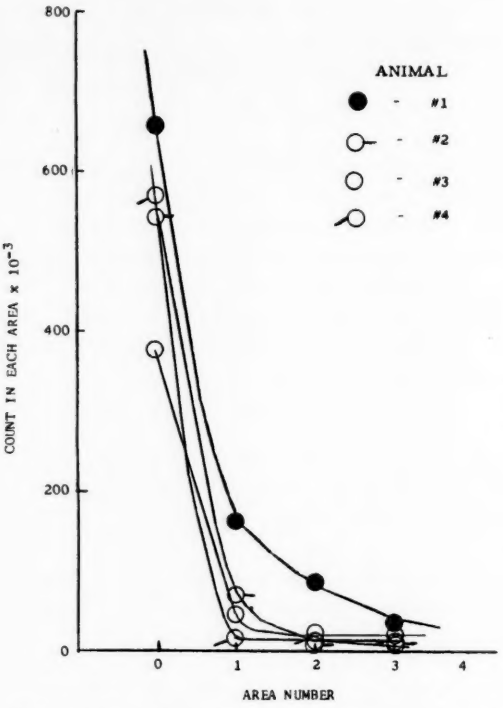


Fig. 1. The total isotope counts as a function of sample area for each test animal.

By means of lead-shielded syringes, eleven guinea pigs received injections. The radioactivity of the injected areas was determined by means of both gamma and beta type counters. The greatest accuracy was obtained when counts were made with specimens placed *in* the noted well-type scintillation counter.

Of the eleven test animals, four were used for an examination of the radial spread of the BGG-I^{131} from the original point of deposition. The remaining seven were used to follow the spread of the BGG-I^{131} through the body.

RESULTS

Each animal was sacrificed at the time of examination, the first, forty-eight hours after the injection, and the others at intervals of twenty-four

hours, for a total of 120 hours. For purposes of studying the radial spread of antigen in the first four animals, the abdominal surface was blocked off into four areas as illustrated. The abdominal skin area represented by the innermost square labeled was first removed and placed aside for a count of its radioisotope content. The second square was then removed and its radioisotope content determined. In a similar manner, the third and fourth areas were studied. When all radioisotope activity was corrected for background count and for radioactive decay, and with the time of injection

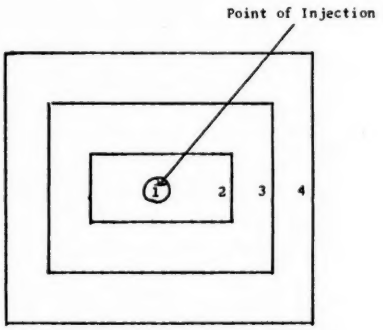


Fig. 2. The numbers represent the squares of tissue successively removed for measurement of radioisotope content.

taken as the common reference time, the total radioisotope counts for the areas removed from the animals were made. These are presented in Figure 1. There was excellent agreement between the various sets of results.

Beginning at forty-eight hours, there was a progressive decrease in radioactivity proceeding from the point of inoculation to the most distal tissue area sampled. At the end of seventy-two hours, the counts obtained from the second, third and fourth areas indicated an almost virtual absence of the antigen from these sites, but not from the original site of the injection (Fig. 2, part 1). This finding was confirmed by the results for 96 and 120 hours.

When the distribution of activity between the original point of injection and distal areas was plotted against the function of time, an interesting relationship became apparent. Figure 3 shows that when the per cent of total radioactivity measured at the site of injection is compared with that of the three more distal areas as determined for a period of five days, there was a relative increase at the former and a decrease to the vanishing point at the latter. At the end of five days, approximately 85 per cent of the radioactivity present was therefore being retained at the site of injection.

The course of dissemination of radioactivity through the body of each animal was determined in the remaining seven test guinea pigs by means of

examinations of liver, spleen, kidneys, lungs, small intestines, brain and blood. The results are shown in Figures 4 and 5.

The greatest radioactivity was noted in the blood and in the kidneys and liver. Considerable amounts were present in the small intestine and the

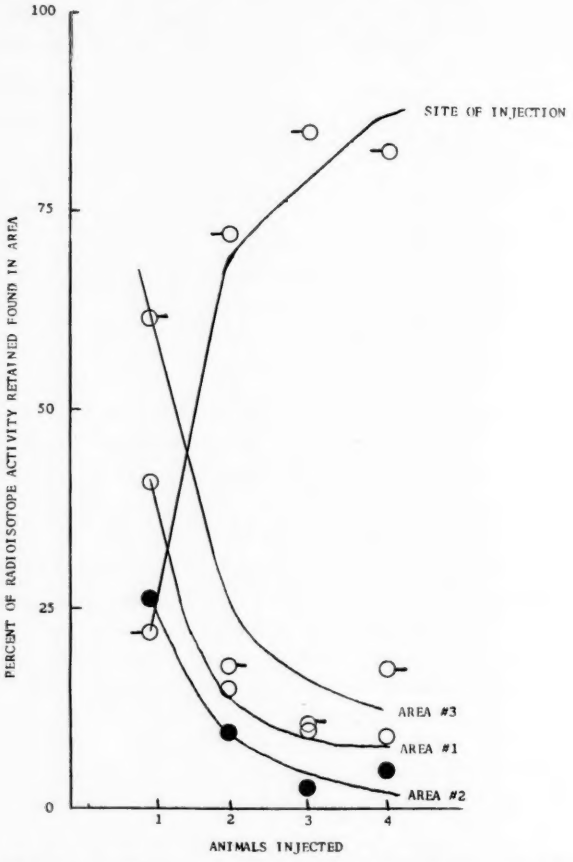


Fig. 3. Distribution of activity as a function of time. (For key to symbols, see Figure 1.)

lungs. The totals measurable in the spleen and brain were negligible in quantity. The first quantitative release of the radioactive antigen as measured from the original point of deposition took place chiefly between six and twenty-four hours after injection. Peak values of radioactivity were then noticeable in the kidneys, the liver, the small intestine and in the lungs at the end of twenty-four hours. Thereafter the amount of radio-

activity precipitously diminished. In the bloodstream the peak concentration occurred within forty-eight hours. There was then a rapid decrease in radioactivity.

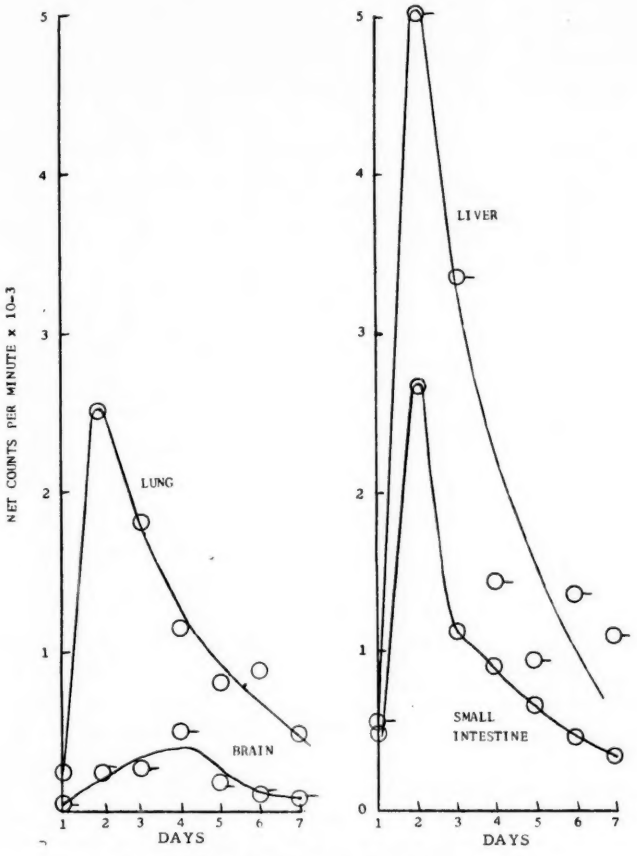


Fig. 4. Activity in organs as a function of time.

DISCUSSION

The results obtained with BGG-I^{131} confirm and extend observations made previously by us with another water-in-mineral oil type of emulsion *(op. cit.)*. In the previous study, the retention at the point of deposition in animal tissues of the water-in-mineral oil type of emulsion was demonstrated clearly by means of an incorporated radiopaque substance.

The high level of radioactivity associated with the blood samples indicated that the spread of the BGG-I^{131} throughout the animal body occurred, as

was expected, by means of the bloodstream. Of that portion of the BGG-I^{131} released from the injection site, the highest blood levels occurred between six and seventy-two hours following the injection. Predictably, therefore,

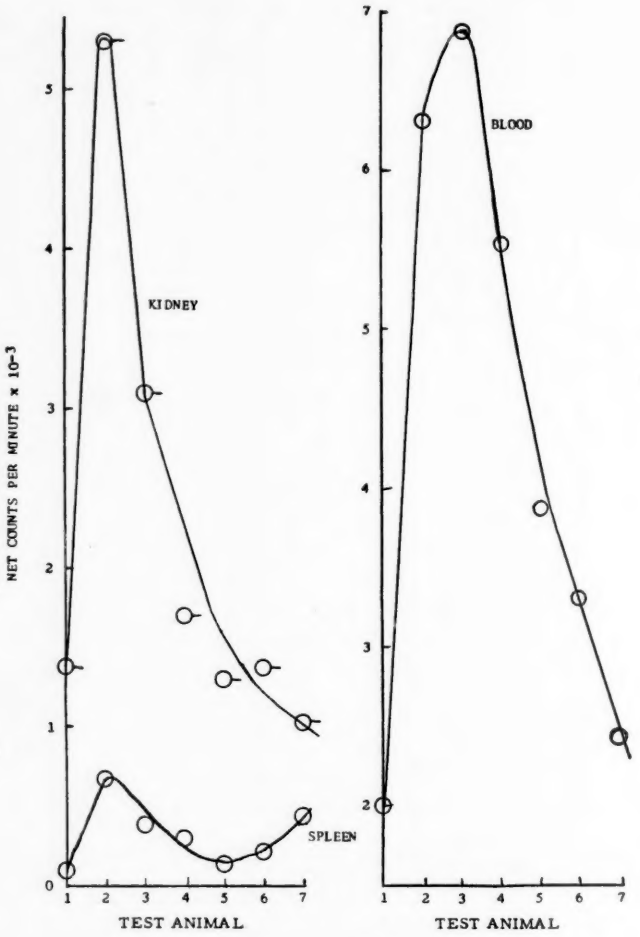


Fig. 5. Activity in organs as a function of time.

the peak levels of BGG-I^{131} in the kidney, liver, small intestine and lung appeared at twenty-four hours and tapered off sharply after this.

The aggregate or spherule formation previously reported for water-in-mineral oil types of emulsions as noted by roentgenograms, suggested a form of mobilization in the tissues. The results of the present study have been

interpreted as indicative of a filtering action by the organs or tissues as the mobilized blood-borne BGG-I^{131} traveled through the body. Evidence for or against the participation of phagocytes was not directly collected. It might be inferred, however, that phagocytes were involved in removing the antigen to the lymphatics and in the initial mobilization of the BGG emulsion in the tissues. A possible role for transport of the BGG to the blood by phagocytes, however, might be presumed. In the absence of supporting evidence, this hypothesis cannot, at this time, by this means be established.

Extrapolation as to the fate of the emulsified extract injected into humans cannot, as a result of this study, be made because of the differences in the sites of the injections, the quantity used and the known differences in circulatory and metabolic rates in animals and in man.

REFERENCES

1. (In press).
2. Brown, E. A.: Opsiphylactic injection treatment of grass hay fever and pollen asthma. VIII. Rev. Allergy & Applied Immunol., 14:302 (May-June) 1960.

AUTHORS' NOTE: *This paper is published as one of a series of studies, and because of experience obtained by the means described, the emulsions discussed here are no longer used. Reports concerning the properties of the new emulsions will appear in the future.*

EDUCATING THE PUBLIC

We must recognize that it is our job to educate the public to some phases of medical care which have previously been highly privileged and therefore undiscussed and unpublicized. We must lead the public to understand that medicine is an art and a science which is not, and never will be, a completely exact, formalized or mechanical procedure. We must teach them to understand that experimentation and risk is always involved. We must do these things, and yet, at the same time, impress them with the high quality of private medical care and the desirability of its administration by private practitioners. We must welcome accurate and factual reporting and we must justify our procedures, and the price we charge for them.—Excerpt from "The Changing Image of Medical Care" by HARRY J. LOYND, President, Parke Davis & Company. (Given at the Michigan Clinical Institute, Detroit, Michigan, March 12, 1959.)

PSYCHOTHERAPY OF PARENTS OF ALLERGIC CHILDREN

HYMAN MILLER, M.D., F.A.C.A., and DOROTHY W. BARUCH, Ph.D.
Beverly Hills, California

THIS PAPER is based on observations emerging out of fourteen years of integrating psychotherapy into the management of allergic children. The senior author has been in a singularly favorable position to do this, practicing as he does both medical allergy and psychotherapy. Since there are many allergic children in his practice, he has, with the cooperation of the co-author, had rich opportunity to observe the emotional inter-relationships between parents and their allergic children and to explore problems that deal with the psychotherapy of parents along with the child.

During the years, we have seen that when the usual medical treatment for allergy fails, the key to a child's improvement often lies in the field of the emotions. The child's first need in this area is to feel that he as a person is loved as he is: with all his varied feelings, the ones he learns to call "bad," as well as those called "good." He fears that if he shows hostility he will be discarded. Therefore, beside the tender loving care that must come to him, we have found that the most important single emotional factor that precipitates or prolongs physical symptoms is the child's repression of anger at his parents.

This requires a word of explanation. As we brought out in an earlier paper,[1] the allergic child characteristically blocks the normal hostility which all children feel at moments toward their parents. When a parent is the target of angry feelings, the child finds it very threatening to own up to this fact. He feels he will alienate his parents. He tries to hide his anger even from himself. He may divert it onto substitute targets, displacing it for instance onto siblings. He may disguise it through misbehavior which troubles his parents. These efforts, however, prove inadequate to relieve inner tension. He then turns to exacerbations of physical symptoms, using his allergic constitution in an unconscious and unsuccessful attempt to establish emotional homeostasis. He turns his own body into the target of his anger, discharging the hostility against himself, punishing himself for feelings which he is ordinarily too afraid to admit to consciousness. Very rarely can the allergic child say with any discharge of affect, "I'm mad at my mother or my father" or elaborate what in fantasy he would like to do to them in his anger. But when he comes to the point where he feels safe in telling about his feelings, then we have repeatedly seen his symptoms decrease.

To feel safe, the child must sense with certainty that his hostile feelings

Presented at the Annual Meeting of The American College of Allergists at the Americana Hotel, Bal Harbour, Miami Beach, Florida, March 4, 1960.

are accepted by an adult in whom he has confidence. A therapist may serve temporarily, but in the end the child must be convinced that his parents "can take it." For he leans and relies most on them, after all.

For this reason, in the regular routine of allergy practice, when an emotional factor is seen to be present, part of our procedure has been to talk with the parents about the fact that hostility-toward-parents is felt normally at times by all children in the process of growing up. We have found it helpful, too, to explain that allergic children have unusual difficulty in expressing this without subterfuge or disguise.

We try to be very sensitive in observing the parents' reactions to these ideas. Some parents respond positively and non-defensively. It is relatively easy to help this group of parents get to the point where they are able to state with sincerity to their child that he naturally is sometimes angry at them. They are able to feel within themselves that this really is natural.

They can, in addition, grasp the idea that a firm differentiation must be made between *feelings* and *actions*. All feelings, even the wishes and fantasies about the often primitive and "gorey" things children would like to do in their anger, must be differentiated from what can really be acted out. It is permissible for instance to talk about feelings, to tell stories or to make pictures of what a child would like to do in his angry moments. These are non-harmful modes of discharge. They do not physically touch the parents. But kicking, hitting, destructiveness or any actually harmful or hurtful acts must be barred. They invariably produce additional fear. "You'd like to but you may not really." This statement and holding to the firm limits of action implied in it is essential in order for a child to feel safe in bringing hostile feelings out.

A small episode illustrates the appreciation of such techniques by one mother. She glances at her watch on the way out after her five-year-old boy has had his injection of antigen. She exclaims, "Oh dear, it's too late to go to the toy store." Her child, as if by accident, pushes his smaller brother. "Here, here," says the mother easily, "I know you're mad at me because we can't go to the store. But you mayn't push your brother instead. You can tell me straight out. . . ." The child glares at her. "I don't like you at all." "I know you don't now," the mother nods, with confirming acceptance.

With this type of acceptance of feeling along with the limiting of hurtful acts, as accompaniment to the allergy treatment, this boy had been clear of asthma for the past year. Allergy treatment alone prior to this had failed.

During the interim, his mother, in her office visits with the child, had been exposed to an informal type of psychotherapy. Her confidence in the allergist had permitted her to talk about herself as well as about the child, and to reach feelings within herself which had hitherto been repressed. She had gotten, for instance, at previously hidden hostile feelings she herself had felt as a child to her parents. With this realization she began to sanction with real conviction her child's feeling of hostility to her. Soon

then in his turn he had begun to feel safe in bringing his feelings out. He knew with equal conviction that she would understand. Then, in her turn, she noticed that his symptoms diminished and she grew more and more able to accept with equanimity the unmasked verbal expression of her child's anger toward her.

In some cases parents reach out for the principles involved in all of this but cannot so readily accept them with emotional conviction. There is rather, a pseudoacceptance, a matter of technique without inner confirmation of feeling. There is a note of insincerity present which the parent may not even realize but which the child invariably perceives. His symptoms in consequence keep recurring. In still other cases, the mere mention that hostility toward a mother or father is possible, proves too disturbing to a parent. In either instance, we can be quite certain that tender spots within the parents' own emotional reservoir have been touched.

Then deeper and more formal psychotherapy is indicated. In most cases, the mother only has entered treatment; in some recalcitrant cases, both parents. In some cases, the child as well has had psychotherapy on a continuous basis; in other cases, the child has had only occasional psychotherapeutic sessions. In still other cases, after the diagnostic sessions, no psychotherapy has been attempted with the child. Recovery, we considered, lay in the psychological readjustment of the parents.

Obviously it is in the cases where the two parents and the child are all in psychotherapy that the nature of the emotional interplay can be best understood. In our office, one of us has worked with one parent, the other of us with the other parent and the child. Some parents have individual therapy only; some have group therapy; some have a combination of both. Active collaboration between the therapists continues constantly. We confer together daily on the same day as the sessions, before the material grows cold. This often reveals how the pieces of the emotional puzzle fit together. It shows the inter-relationships not only of events but of feelings and fantasies, and it often contributes therapeutic leads.

In the past fourteen years we have had many allergic children with one or the other parent in psychotherapy. In ten families, however, we have had both mother and father in intensive treatment. In fifteen additional families where the mother (or in two cases the father) has been in continuous therapy, we have had enough contact on an occasional basis with the other parent to get insight into his psychodynamics. It is from these twenty-five families (involving twenty-nine allergic children), where we have been able to study both parents psychologically in an extended and intensive way, that the following material is drawn.

Among the twenty-nine children involved there were twenty with asthma as the dominant allergic syndrome. (One of these had equally severe allergic neurodermite.) The remaining nine children had hay fever as the dominant allergic syndrome. It should be pointed out here, however, that even though there is usually the one dominant syndrome, we find periods

when the major syndrome is replaced by or complicated by a severe exacerbation of what is usually a minor syndrome. Such shift in symptoms we have found to be connected often with shifts in fantasies that are unconsciously shared by parents and child.

In the tremendous mass of interwoven material involved in these cases, there stands out clearly the fact that the parent unconsciously makes use of the child for his own emotional purposes. He often unconsciously wants to have the child retain his symptoms. The child in turn unconsciously wants to keep them. The illness often becomes the place where the unrealistic purposes of parent and child coincide.

A case report here will serve to illustrate this. In the family of the boy with asthma and neurodermite, the mother as a child had many times heard it said that she'd not been wanted. In her loneliness she turned to her older brother. For one thing, during her childhood and his adolescence she had extensive sex play with him and would enjoy—as she put it—"getting his mess all over her. It made us more like one person," she said. "Both of us cruddy." "Without my brother I was a nothing," she said, "I thought I'd die if we were ever separated. He was like a part of me or I of him, we were so attached. When he got married and left me I think I wanted to kill him." On a deep level, the attachment to her brother represented a symbiotic relationship which she felt she could not do without.

When she married she strove unconsciously to make her husband into a brother whom she could keep with her always. When her child was born, however, her husband was very preoccupied with business, for unconscious reasons of his own, and once more she felt abandoned. So she turned voraciously to her child and fantasied him almost like a part of herself which she would never have to lose.

When she first brought him into the office at the age of two years and three months, she was strangling him literally, clutching him so tightly to her. On his side, he was clinging, one arm down inside the neckline of her dress, his hand digging into her breast. He was wheezing heavily and was slightly cyanotic. The skin eruption was extremely severe. Both symptoms had started when his mother had needed to wean him at nine months and allergy treatment had then been instituted. As she realized later, at this time she had been very disturbed at the child's growing old enough to necessitate the separation from her breast. Recently, however, the skin eruption and asthma had both become far more severe. This had happened when she recognized that she was again pregnant. She fantasied the new pregnancy as an intrusion—something that threatened to separate her more from her boy.

When the psychotherapist reached for the child to take him into the playroom, she protested the separation. "But *I've* got to carry him," she said. Still later she saw that what she had wanted even more deeply was to be carrying him inside her. She wanted none of him as a growing-up individual who might leave her as her brother had. The eczema helped

her identify him as the "messy" brother she had "owned" earlier. The asthma gave her the excuse she needed for holding him to her. "So close," she said, "that I try to breathe for him."

The father encouraged this, for the pattern helped also to satisfy his fantasies. A critical experience in his childhood had been the death of his mother after a prolonged illness, during which she had repeatedly said to him, "I'll never live to see you grow up." Frightened, he wanted, as he put it, "time to stand still" so he could keep his mother. He did not want to grow up.

When he married, he thought of his wife as a girl friend. They were two youngsters having sex play together. Suiting both their fantasies, their sexual pattern concentrated on foreplay, and intercourse, in general, was incomplete. When she unexpectedly became pregnant with the boy and was tired and listless, it reminded him too much of his mother when she had been ailing and sick. It was at this time he ran from his wife into his work.

Then, after his son was born, he fantasied the child as himself and his wife as his young mother before she'd become ill. As long as his son remained a baby, needing to be held, diapered and cleaned up, the father was content. He didn't want the child to mature any further. For if he did, it would prove that time had not stood still. The persistence of the eczema after the child's infancy then served the father's unconscious purpose. By identifying with the eczematous "mess," the father did not grow old either.

Thus the child through his physical symptoms fed the fantasies of both his parents. And yet, even though he wanted the closeness as they did, he felt the smothering quality that came from his mother. It went against his natural striving for independence. And so, it also made him angry. But this he dared not express for fear of the separation and abandonment he felt would come as result. In his play therapy he showed the conflict in his feelings. He would curl up like a baby inside its mother, saying, "This is my goodest way to be." But then he would fantasy being smothered and would start to wheeze. As time went on he would crawl repeatedly into a nest of pillows, his wish to "go in" matching his mother's wish to still have him inside her. Then he would throw aside the pillows and would stamp on them madly, saying, "You, you, you terrible witch, you're not going to capture me and keep me where I can't breathe." Moreover he would act out her wish to have a "messy" relationship. He would get undressed and immerse himself in a tubful of clay, rubbing it over himself, pretending to be a mother rubbing her messy baby.

With longterm psychotherapy, the mother was able to give up her symbiotic fantasies of boy-inside her or part-of-her. Concommitantly she became able to accept the child as a separate person who was entitled to his own feelings of hostility to her. With this his asthma stopped, recurring only at extremely rare intervals when his mother regressed.

Meanwhile, the fantasies associated in the child's mind with the skin

eruption gradually moved from the mother to the father. He imagined playing baseball with his father. In these games he would throw "mud" or "pooch balls" at his father, "messing him all up." Thus, in his mind too, his father and he both became babies and time stood still.

At other moments, he fantasied attacking his father tooth and nail and eating him up to get his "strongness," as he put it. Through messing and clawing at his own skin, he continued to court and fight his father, satisfying the father's still persisting desire to stay young through him, and at one and the same time trying in his own fantasy to "scratch out his father," but then, in typically allergic fashion, turning the hostility onto himself.

Finally, the father who had come into therapy later than his wife, began to let time take its stride. On his part, he became acceptant of his child as a child with feelings that were at times naturally hostile. With this the child's skin eruption markedly improved.

In another case, more briefly, an asthmatic mother wanted her little asthmatic girl of three to act out for her the "little mad demon" she herself had not dared to be. One of her own persistent fantasies reaching up from childhood was of her mother drowning and her father showering her with all the gifts he ordinarily gave to her mother. Then, however, she would grow panicky, would want her mother back but would fear that her mother would be angry at her. At this point in her still recurring fantasies she would shift her daughter into the role of returning mother whose anger she feared. And so, although she would with one side of her stir the child into outbursts of the little mad demon, she would with the other side of herself, back frantically away from any anger which the child-mother-figure openly directed at her. She would find her own way out of her emotional dilemma by retreating into asthma herself.

When her husband would start to show his affection toward their child, she would fiercely snatch her away. She could not stand her fantasied mother being preferred.

On his side her husband did not protest this. For to him his wife represented his mother protecting him from further injuring a younger sibling whom he had actually hurt as a child.

In her turn, the child was angry at her mother for coming between her father and herself. In her sessions she showed that her fantasies coincided with her mother's. She played that she wanted to drown her mother, would grow frightened, then would talk as if she were drowning herself and would develop asthmatic attacks.

These persisted until her mother became more able to receive her hostility without putting the alternating pictures of her own "demon" and her own mother onto her.

Incidentally, in this case, as one would suspect, a major reason for the mother's long concentration on the child was to avoid making a relationship with her husband whom she took as the father she felt guilty about having wanted earlier. This too needed working through in order for the mother

to give up her hostile dependent attachment to the child and to become able to accept her child's hostility.

To cite some of the fantasies from just one more family: The mother often took her asthmatic son (almost four when her therapy started) as her younger brother whom she had recurrently dreamt of throwing out of the window. "I see him lying on the ground," she said. At other times she took him as the father whom she had wanted to own.

Her husband on his part had lost his father in infancy and had slept in his mother's bed until his late teens when she had died. When his own son was born, he was disturbed. He unconsciously wanted any other child out of the picture in order to remain the only child himself. He also feared the child's growing older and becoming an adult rival, although he ambivalently wished that the boy might take the role of husband rather than himself. For, he still carried inside him the old fear that a wife must kill a husband as he had fantasied his mother had killed his father in order to take him into her bed.

The boy felt the frightening countercurrents and grew deeply angry. He dreamed of throwing his father out of the window. "I see him lying on the ground," he said, dramatically using the very same words as his mother had used. "No," he said, "That's not the father on the ground, that's the boy lying on the ground." And he would wonder in great bewilderment, "Who throwed him?" And then as if he had actually shared his mother's dream, "Did the mother throw the little boy out?"

He feared this would happen to him should he show his anger. He wanted his mother to throw his father out for him and grew angry at her for not doing so. But instead of expressing his anger directly, he got sick with asthma. Apropos of this, when he was seven, he said, "When I'm sick I'm just a poor little helpless child and nobody'll have the heart to throw me out."

As the mother and father became aware of these and other fantasies, they became able to sanction and accept the child's verbal expressions of hostility, yet at the same time to limit the acting out. And the asthma cleared.

From the mass of data in our cases, we can draw some generalizations concerning psychotherapy with parents of severely ill allergic children. The parents in this group are themselves severely ill emotionally. Psychotherapy with them is long and involved. It is usually important that it go on even after the child is improved. Otherwise regressive patterns in the parents continue and create recurrent pressures for the child.

Since their inability to relate well to each other in marriage abets their turning to the child, therapy needs to help them become able to invest a healthy amount of emotional energy in working on the marriage relationship. Often they cannot accept the child's hostility because to them the child represents themselves, and they cannot accept the anger they felt toward their own parents with its concommitant fantasies when they were small. Often their child represents to them a parent to whom they were

hostile and yet attached. Then the child's hostility seems to them like rejection from a parent. Often the mixed animosity and clinging wishes they feel toward the child lead them to make a show of loving him, particularly of overprotecting, of giving him whatever he wants. Limitations and forbiddings seem "too cruel," especially because underneath such forbiddings lie their own explosive hostilities.

When a parent can give up the child as part of himself, when a parent can give up the child in the image of his own parent, when the parent has become able to love the child maturely, then he can let the child be himself and grow as himself and speak for himself, as he feels in all honesty, then the allergic symptoms no longer are needed to serve mutual purposes. The child can then make better use of his allergy treatment to get well.

201 South Lasky Drive

REFERENCE

1. A Study of Hostility in Allergic Children. Am. J. Orthopsych., 20:506, 1950.

PHILOSOPHY IN INTELLECTUAL DEVELOPMENT

Philosophy is a stage in intellectual development and is not compatible with mental maturity. In order that it may flourish, traditional doctrines must still be believed, but not so unquestioningly that arguments in support of them are never sought; there must also be a belief that important truths can be discovered by merely thinking, without the aid of observation. This belief is true in pure mathematics, which has inspired many of the great philosophers. It is true in mathematics because that study is essentially verbal; it is not true elsewhere, because thought alone cannot establish any non-verbal fact.

Savages and barbarians believe in a magical connection between persons and their names, which makes it dangerous to let an enemy know what they are called. The distinction between words and what they designate is one which it is difficult always to remember; metaphysicians, like savages, are apt to imagine a magical connection between words and things or at any rate between syntax and word structure. Sentences have subjects and predicates, therefore the world consists of substances with attributes. Until very recently this argument was accepted as valid by almost all philosophers; or rather, it controlled their opinions almost without their own knowledge.—Bertrand Russell. From "Philosophy's Ulterior Motives" in *Unpopular Essays,* Simon & Schuster, Inc., 1950.

ORAL DECONGESTANT THERAPY IN ALLERGIC RESPIRATORY DISEASES OF CHILDREN

ARTHUR LIPSCHUTZ, M.D.
Philadelphia, Pennsylvania

THE MANAGEMENT of allergic respiratory diseases in children has involved many types of local decongestant drugs as well as antihistaminics and bronchodilators. Many undesirable side-effects, aggravated allergy, and drug habituation have been produced by this therapy.

Specific measures of environmental control and hyposensitization provide the most effective treatment of allergic disorders, but these measures do not promptly eliminate symptoms in a considerable number of patients. During the past few years, sympathomimetic drugs, which were previously used locally to decongest the nasal mucosa, have gained therapeutic recognition in oral administration.

It is our purpose to discuss the oral use of the sympathomimetic drugs in the therapy of allergic respiratory disease in children, and to present the results of a double-blind study with one of the sympathoamines, d-pseudoephedrine, a stereoisomer of l-ephedrine.

MATERIALS AND METHOD

The double-blind study was carried out in 200 children between the ages of four months and seventeen years using pseudoephedrine,* the antihistamine triprolidine combined with pseudoephedrine†, and a placebo. The children were from the Philadelphia Municipal Welfare Center, a school for orphaned boys, the Pediatric Allergy Clinic of the Hahnemann Medical College and Hospital, and Pediatric Ward Patients at St. Luke's and Children's Medical Center.

All children with respiratory disorders were given one of the above preparations four times daily for a period of three days. The drugs labeled with a code number were sent to us from the manufacturers and were prepared in such a manner that the nurses, physicians, and patients could not distinguish between the placebo and the active drugs. Records, which included provisional diagnosis, dates the drug was initially administered and terminated, clinical course, laboratory data, results of treatment, and complications, were kept of all children. No other drug therapy was employed.

We gathered data on 148 children with an initial diagnosis of non-allergic respiratory disease categorized as pharyngitis, tonsillitis, coryza, upper re-

---

Presented at the Annual Meeting of The American College of Allergists at the Americana Hotel, Bal Harbour, Miami Beach, Florida, March 3, 1960.

*"Sudafed"® brand Pseudoephedrine Hydrochloride, Burroughs Wellcome & Co., Tuckahoe, New York.

†"Actifed"® Tablets and Syrup, Burroughs Wellcome & Co., Tuckahoe, New York.

TABLE I. RESULTS OF THERAPY IN ALLERGIC VS. NON-ALLERGIC PATIENTS

	Symptomatic Relief	Pseudoephedrine with Triprolidine	Pseudoephedrine	Placebo
Allergic respiratory diseases	Excellent	20% (5)	24% (4)	0% (0)
	Good	68% (17)	65% (11)	40% (4)
	Poor	12% (3)	11% (2)	60% (6)
Total		(25)	(17)	(10)
Non-allergic respiratory diseases	Excellent	16% (8)	14% (9)	21% (7)
	Good	51% (25)	54% (35)	35% (12)
	Poor	33% (16)	32% (21)	44% (15)
Total		(49)	(65)	(34)

Figures in parenthesis indicate actual numbers of patients.

spiratory infection, tracheobronchitis, sinusitis, and pneumonitis. From the pediatric allergy clinic, we used another fifty-two children who suffered from nasal allergy (seasonal and non-seasonal), bronchial asthma, asthmatic bronchitis, and atopic dermatitis associated with allergic rhinitis. All 200 children received coded drug, and the therapeutic results were evaluated before breaking the code. The drug response of the patients was judged as "excellent," if relief was complete or virtually so; as "good," if relief was obvious, but only partial, and as "poor," if little or no relief resulted.

RESULTS

In brief, these data (Table I) indicate that pseudoephedrine, with triprolidine or alone, gives satisfactory results in almost 90 per cent of the allergic conditions, as well as in almost 70 per cent of the non-allergic conditions. In order to show which diseases responded best, Table II presents the data according to the degree of relief obtained in each disease.

TABLE II. CLASSIFICATION OF RESPIRATORY DISEASES ACCORDING TO DEGREE OF DRUG RELIEF OBTAINED

	Excellent	Good	Poor
Pseudoephedrine with triprolidine	Cory. 2	Cory. 10	Phar. 7
	Trac. 3	Trac. 13	Tons. 6
	B.A. 5	B.A. 10	B.A. 1
	Pneu. 3	Pneu. 2	N.A. 2
		A.B. 4	Cory. 1
		N.A. 3	Pneu. 2
Placebo	Cory. 4	Cory. 5	Phar. 8
	URI 2	URI 4	Tons. 5
	Phar. 1	Phar. 2	Sinu. 2
		Trac. 1	B.A. 4
		N.A. 1	A.B. 2
		A.B. 3	
Pseudoephedrine	Trac. 5	Trac. 9	Cory. 4
	Cory. 2	Cory. 6	Phar. 8
	Phar. 2	Phar. 3	Tons. 7
	N.A. 2	URI 3	Sinu. 2
	A.B. 2	Sinu. 5	A.D. & N.A. 2
		Pneu. 5	
		Tons. 4	
		N.A. 6	
		B.A. 4	
		A.B. 1	

Key for Table II: A.B.—allergic bronchitis, A.D.—atopic dermatitis, B.A.—bronchial asthma, Cory.—corvza, N.A.—nasal allergy, Phar.—pharyngitis, Pneu.—pneumonitis, Sinu.—sinusitis, Tons.—tonsillitis, Trac.—tracheobronchitis, URI—upper respiratory infection.

During the evaluation of the respiratory diseases and their response to the drug used, we discovered eight cases of allergic respiratory disease in the group of 148 children, all of whom were originally thought to be non-allergic. The underlying allergy was suggested by a history of previous respiratory complaints and a favorable response to the drug. The diagnosis of the allergic state was further confirmed by an eosinophilia and positive reactions on skin testing. More detail on these eight patients is presented in Table III.

The writer is impressed that children with coryza-like symptoms who respond to oral decongestant drugs should be suspected as being allergic until proven otherwise.

TABLE III.

Names	Age Years	Sex	Chief Complaint	Diagnosis	Laboratory Data	Drug	Results
1. R.G.	6	M	Runny nose	Cory.	454 TE Pos. dust	P	E
2. M.G.	13	F	Itchy skin Runny nose	Cory. A.D.	525 TE Pos. food and dust	P&T	G
3. W.J.	5	F	Barking cough	Trac.	350 TE Pos. dust and molds	P&T	G
4. S.G.	7	M	Runny nose	Cory.	410 TE	P	G
5. B.P.	7	M	Nose bleeds	Cory.	400 TE Pos. dust and grass	P&T	G
6. E.P.	14	M	Post nasal drip	Sinu.	605 TE Pos. dust and cat hair	P	G
7. B.T.	10	F	Barking cough	Trac.	376 TE Chest film Pos. dust and molds	P&T	G
8. T.W.	16	M	Post nasal drip	Sinu.	Sinus film	P	G

Key for Table III: Trac.—tracheobronchitis; Sinu.—sinusitis; P&T—pseudoephedrine with triprolidine; P—pseudoephedrine; E—excellent; G—good; TE—total eosinophils per cubic mm.; Pos. dust, molds, cat hair, food—positive intradermal skin test reactions; Chest and Sinus film—roentgen evidence of asthmatic bronchitis or pansinusitis.

DISCUSSION

McLaurin,[1] in commenting about surveys on the use of oral decongestants, feels that anyone who has a respiratory disease over any length of time is apt to become bacteriologically sensitized. Oral decongestant drugs will cause shrinkage of all nasal and sinus tissues and seem to be usefully employed in all nasal conditions in which such sensitization has occurred. This has been borne out in our observation.

Ten years ago Fabricant[2] stated that the problem of producing new sympathomimetic amines was of great importance in reducing the incidence of vasomotor rhinitis medicamentosa.

For many years nose drops and antihistaminics were used for all children with coryza-like symptoms and nasal "stuffy nositis." Fabricant found that nasal vasoconstrictors possessing an unusually high alkaline pH value may disturb the normal nasal pH level present in clinically normal nasal passages, enhance irritation of the mucous membranes, and postpone the return of the nasal mucous membranes from a pathological alkaline status to a normal, slightly acid status. The introduction of oral sympathomimetic drugs has done much to overcome the untoward effects of topical nasal decongestants and reduce the discomfort associated with the use of nose drops in children.

Oral nasal decongestant drugs have been reported to be successful in the

treatment of acute and subacute rhinitis, vasomotor rhinitis, nasal congestion, allergic rhinitis, and postnasal drip. Antihistamines, also useful in these conditions, have been combined with sympathoamines to yield drugs of greater effectiveness. The actions of tripolidine and pseudoephedrine are shown in Figure 1.

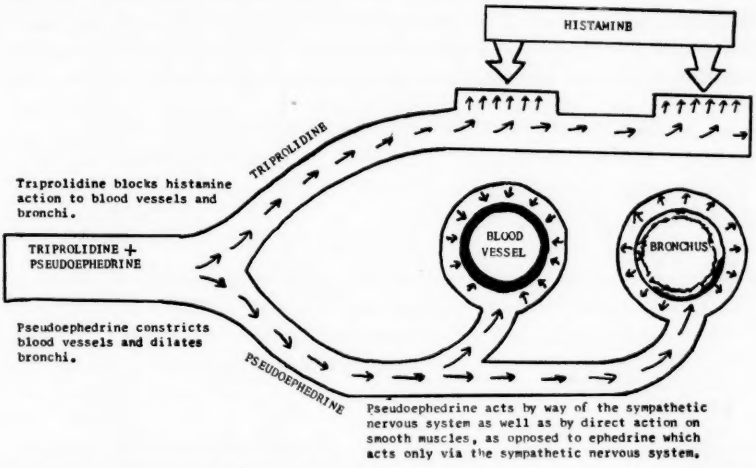

HISTAMINE
TRIPROLIDINE
Triprolidine blocks histamine action to blood vessels and bronchi.
TRIPROLIDINE + PSEUDOEPHEDRINE
BLOOD VESSEL
BRONCHUS
Pseudoephedrine constricts blood vessels and dilates bronchi.
PSEUDOEPHEDRINE
Pseudoephedrine acts by way of the sympathetic nervous system as well as by direct action on smooth muscles, as opposed to ephedrine which acts only via the sympathetic nervous system.

Fig. 1. Diagrammatic figure illustrating action of pseudoephedrine, triprolidine, and triprolidine with pseudoephedrine.

An understanding of the physiologic basis of nasal congestion and rhinorrhea and the use of oral sympathoamines is pertinent.[3] The nasal mucosa is innervated by both parasympathetic and sympathetic nerve fibers. The parasympathetic nerve fibers leave the brain stem with the facial nerve, pass through the geniculate ganglia, and then form the greater superficial petrosal nerve, which passes to the sphenopalatine ganglia. From there, postganglionic fibers travel with the deep branch of the maxillary division of the trigeminal nerve to the nasal mucosa.

Balancing this parasympathetic innervation of the nose is the sympathetic innervation, which arises in the upper thoracic segments of the spinal cord. From here, preganglionic fibers pass by the way of the stellate ganglia to the superior cervical ganglia where they become postganglionic, then to the carotid plexus and into the sphenopalatine ganglia, and then to the nasal mucosa with the maxillary division of the trigeminal nerve. In conditions of normal nasal physiology, the parasympathetic and the sympathetic systems operate in a state of balance. Any pathologic conditions which tends to reduce or increase the activity of one of these systems without similarly affecting the activity of the other results in an imbalance between the neurohormonal outflow of adrenergic substances of the sympathetic system and acetylcholine of the parasympathetic system. The overactivity of the para-

sympathetic system caused by the production of acetylcholine has the effect of stimulating the glands of the mucous membrane of the nose, at the same time increasing the turgor of the turbinates. If the parasympathetic outflow is uninhibited or increased by pathologic conditions, a congested and running nose results. If the parasympathetic innervation is decreased or the sympathetic innervation stimulated, the reverse effect takes place. There is vasoconstriction, with decreased activity of the mucous glands of the nasal mucosa, and the nose is wide open and dry. The sympathomimetic nasal decongestant drugs can be classified as shown in Table IV.

TABLE IV. SYMPATHOMIMETIC NASAL DECONGESTANT DRUGS

Generic and Brand Names	Chemical Structure		Other Major Clinical Uses P=Pressor B=Bronchodilator C=CNS Stimulant
1. Phenylephrine USP (Neosynephrine)	3-OH	OH CH_3	P
2. Hydroxyamphetamine USP (Paredine)	4-OH	CH_3	P
3. Methoxamine USP (Vasoxyl)	2-CH_3O 5-CH_3O	OH CH_3	P
4. Ephedrine USP		OH CH_3 CH_3	P B C
5. Pseudoephedrine (Sudafed)		OH CH_3 CH_3	B
6. Phenylpropanolamine NNR (Propadrine)		OH CH_3	P C
7. Propylhexedrine USP (Benzedrex)	Cyclohexyl	CH_3 CH_3	
8. Cyclopentamine NNR (Clopane)	Cyclopentyl	CH_3 CH_3	P
9. Naphazoline NF (Privine)	2-(Naphthylmethyl) imidazoline		
10. Tetrahydrozoline NNR (Tyzine)	2-(Tetrahydro-naphthyl) imidazoline		

Aviado[4] found d-pseudoephedrine, a stereoisomer of l-ephedrine, produced less pressor effect than ephedrine in the laboratory animal. He measured intranasal pressure and carotid blood flow in anesthetized dogs injected with different sympathomimetic drugs. Pseudoephedrine manifested equal reduction of carotid blood flow and nasal pressure (nasal decongestion and carotid vasoconstriction). The relative intensities of both responses may be different, and some drugs can even cause a paradoxical increase of one or both (nasal congestion and/or carotid vasodilatation).

Feinberg[5] found that in seventy-six children with seasonal hay fever who were not responding well to drug therapy, forty-four had excellent to good results when given pseudoephedrine with triprolidine hydrochloride. Developed in Europe, triprolidine has been found to be a potent antihistamine, and when combined with pseudoephedrine, was found to be effective in a significant percentage of the stuffy noses usually not responsive to antihistamines alone, and often not yielding to pseudoephedrine alone. In nonseasonal antihistamine resistant groups, thirty-one out of seventy children had satisfactory relief in Feinberg's observation.

In our double-blind study, twenty-two out of twenty-five patients with allergic respiratory disease responded to pseudoephedrine combined with triprolidine, while thirty-three out of forty-nine patients of non-allergic

respiratory disease responded favorably. Fifteen allergic children out of seventeen showed response to pseudoephedrine alone, while forty-four out of sixty-five non-allergic children gave satisfactory results. Eight children were found to have underlying allergy which was detected because of response to the sympathomimetic drug and the history of previous respiratory complaints with an eosinophilia and positive skin tests.

All patients took medication without any ill effects, and no abnormal urinary or hematological findings were observed. Information regarding the drug response as a nasal decongestant was obtained by subjective observation. We feel the need for better objective methods in evaluating nasal decongestion. Children suffering from blocked nasal passages very often go unnoticed. This occurs because when only the nose is involved, conscious breathing through the mouth may alleviate the nasal congestion for a period of time.

Temperature testing of the nasal mucosa for evidence of vasoconstriction and vasodilatation, and attempts at smearing mucosal surfaces of the nose using technique of the Papanicolau smear have recently been undertaken in an attempt to study objectively nasal congestion and its relation to allergy, and will be reported at some future date.

Oral nasal decongestion has proven to be an effective means of relieving the stuffy nose without any ill effects, and can be useful in directing our suspicions toward possible underlying respiratory allergy in children.

SUMMARY

1. Oral decongestant drugs are effective in treating allergic respiratory diseases of children.

2. Allergic rhinitis responds to oral sympathomimetics without the local rebound phenomenon or chronic stuffy nose frequently caused by topical sympathomimetic drugs.

3. Eight cases of allergic respiratory disease were diagnosed in a group of children originally thought to be non-allergic. The favorable response to the drug therapy coupled with the history of previous coryzal complaints made us suspect underlying allergy, which was subsequently confirmed.

4. Pseudoephedrine, and triprolidine with pseudoephedrine are effective decongestant drugs when used in respiratory allergic and non-allergic diseases of children. There were no untoward effects in the use of these drugs.

REFERENCES

1. McLaurin, J. W.: Personal correspondence.
2. Fabricant, N. D.: Oral, nasal, decongestion. Eye, Ear, Nose & Throat Month., 37:460, 1958.
3. Gordon, J. S.: The use of oral vasoconstrictors in rhinology. North Carolina M. J., 13:24. 1952.
4. Aviado, D. M., et al: A comparative study of nasal decongestion by sympathomimetic drugs. A.M.A. Arch. Otolaryngol., 69:598, 1959.
5. Feinberg, S. M., et al: Actifed, a combination of pseudoephedrine with an antihistamine in the symptomatic treatment of resistant allergic rhinitis. J. Indiana State M. A., 52:2137, 1959.

230 North Broad Street

OCCUPATIONAL BRONCHIAL ASTHMA IN A BAKER DUE TO ASPERGILLUS

A Case Report

AARON WEINER, M.D.
Fair Lawn, New Jersey

A FORTY-NINE-year-old baker was examined on May 7, 1958. At that time he gave the following history:

He began working in the bakery where he is presently employed in 1934. He was well, except for occasional colds and a "cigarette cough," until the winter of 1950 when he began to wheeze. At first these episodes were short and mild. During the summers he was asymptomatic. Each winter the episodes became more prolonged and more severe. After a few years, it became apparent that most of his severe attacks occurred on Saturday mornings. The patient then recalled that every Saturday morning he routinely used flour as a duster in making rolls. He made a dough mixture (heavy flour exposure) and the shop was completely swept and cleaned, raising a large amount of dust. He also recalled that every time he went into the mixing room, he sneezed and then wheezed, especially when the sifter was in operation. During April, 1957, when this condition became severe, he stopped working in the bakery on the advice of his doctor. During this three-week period away from the bakery he had no asthma at all. For two years, up to the time of his first visit, he was desensitized with stock baker's dust extract. This treatment was entirely ineffectual. At the first visit, during May, 1958, he had already returned to work, and his recurring asthma was as severe as before his vacation.

Physical examination revealed: blood pressure—116/80, heart—essentially negative, lungs — slight hyper-resonance throughout, inspiratory and expiratory wheezing with moderately prolonged expiration. The nasal mucous membranes were edematous and pale and there was a small polyp on the right side. On fluoroscopic examination, there were diminished excursions of the ribs. The diaphragm was depressed and had markedly diminished movement on respiration. There was hyper-illumination of both lung fields. The bronchovascular markings were greatly increased. There was no evidence of pulmonary infiltration. An x-ray film of the chest confirmed the above findings.

The following intradermal tests were done:

House Dust—moderate
Wheat 1000 pnu—negative
Rye 1000 pnu—slight
Oats 1000 pnu—negative
Alternaria 100 pnu—negative
Aspergillus 100 pnu—marked plus
Penicillium 100 pnu—negative
Hormodendron 100 pnu—negative
Monilia 100 pnu—negative
Helminthosporium 100 pnu—negative
Cephalothecium 100 pnu—marked plus

The aspergillus extract used is a mixture of A. Fumigatus, A. Glaucus and A. Flavus.

Read at the meeting of the Association of Allergists for Mycological Investigation at the Southwest Allergy Forum, Oklahoma City, Oklahoma, April 2-5, 1960.

Dr. Weiner is Associate Attending Physician and Chief, Allergy Clinic, Barnert Memorial Hospital, Paterson, New Jersey.

After the first examination he improved, as he usually did during the summer. He returned on September 13, 1958. During this four-month interval, the bakery had moved from its old quarters to a new building in another part of the city. All utensils and machines, including the mixers, were replaced. Although he complained of a cough since the cool weather had set in, he had no particular difficulty when he went near the mixers.

Physical examination revealed the usual asthmatic breathing. Complete intradermal testing was done for all the inhalants and the cereals. The significant reactions were to house dust and to several of the molds. The test with aspergillus 100 pnu gave a marked reaction and a delayed local reaction on the following day. There was also a marked reaction to cephalothecium roseum 100 pnu on three occasions. The remaining inhalant tests were negative.

The patient then brought me the following materials in small sterile paper bags: (1) sweepings, (2) rye flour directly from the sack, (3) scrapings from the mixer. These were cultured on three Sabouraud slants which grew aspergillus as the predominant mold. Each slant also contained several colonies of penicillium and a few unidentified colonies.

Indirect testing (passive transfer) was definitely positive for aspergillus and cephalothecium roseum. The cereals and the remaining molds were negative.

On October 30, 1958, spirometry, with a Collins Respirometer, was done. He felt quite well that morning. After a sniff of talcum, the vital capacity, timed vital capacity and the maximum breathing capacity were essentially within normal limits. The patient then sniffed some aspergillus fumigatus powder from the end of a toothpick. Within fifteen seconds, he coughed and within a minute (there was barely time enough to insert the mouthpiece of the respirometer), he had severe asthma. The tracing, when the maximum breathing capacity test was attempted, showed marked trapping which, fortunately, eased off very quickly when the test had to be abandoned in a few seconds. Two injections of epinephrine 1-1000, 4/10 cc each, were then required to abort the attack.

An autogenous dust extract made up from the samplings from various parts of the bakery was prepared. Treatment with this extract and a mixture of the molds found positive on skin testing was started on December 22, 1958, and has been continued up to the present time.

Since the start of desensitization treatment from December, 1958, to January, 1960, the patient has improved. Before treatment, he had almost continual wheezing during the winter months and had to take frequent vacations. During the course of treatment moderate asthma occurred only after heavy flour exposure and responded well to an injection of epinephrine. He has lost no time from work.

During January, 1960, at the suggestion of Dr. Homer Prince, the patient was tested with several species of aspergillus T 33 extracts, supplied by Hollister-Stier Laboratories. The following reactions were obtained:

	1-100,000	1-10,000	1-10,000
A. Flavus	sl. mod.	mod.	mod.
A. Fumigatus	sl. mod.	mod.	mod.
A. Nidulans	mod.	mkd.	mkd.
A. Glaucus	sl. mod.	mkd.	mod. plus
A. Niger	neg.	neg.	neg.
A. Sydowi	mkd.	mkd.	mkd. 1 plus
A. Terreus	mkd.	mkd.	mkd. 2 plus

During the past two months a mixture of the above species of aspergillus, with the exception of A. Niger, was added to the current desensitization treatment. Even though the increments are small, there is a wheal and flare following each injection.

Coincidentally, there has been further improvement in the patient's asthma. The heavy exposures noted above do not affect him as much as previously.

DISCUSSION

Tuft[2] has stated, "In patients with definite positive reactions (to the molds) attempts should be made to determine the clinical significance of these reactions by correlating them with the patient's symptoms or by clinical trial, especially with the nasal test." Maunsell[3] thinks that a "practical approach might be made by confirming one or two positive skin tests in particular patients by inhalation tests." Because of the severity of the asthma induced by inhalation of A. Fumigatus powder, it appeared too hazardous to confirm the clinical significance of the positive reaction to cephalothecium by nasal test.

Noteworthy is the observation that when the bakery was moved to new quarters and much of the equipment was replaced, the patient's condition improved, but only for a few months. When the mold contaminant spread throughout the bakery, his symptoms recurred. The remedy will be found, most likely, in Bonnevie's[1] observation, "The technical prophylaxis through better equipment, good ventilation and housekeeping is the only way to combat this evil of the bakery profession."

During the past ten years, we have been testing all our patients with a series of molds. We have found that, when the intradermal test for aspergillus was marked, a large positive test was also obtained with C. Roseum. This suggests antigenic relationship. Exhaustion of site studies should be done to determine such a relationship. There is no clinical evidence of sensitivity to C. Roseum in this patient. However, C. Roseum was added to the mold treatment mixture since its clinical importance has not been disproved.

Several Sabouraud plates were exposed for fifteen seconds in each of four modern bakeries during working hours. Numerous colonies grew on all the plates. Aspergillus and penicillium predominated. This would indicate that mold exposure in the average bakery is heavy. This is in accordance with the findings of Van der Werff.

If a meticulous allergic survey were conducted on every baker who has bronchial asthma, more cases of occupational mold allergy would be found.

SUMMARY

The following findings support the diagnosis of bronchial asthma due to inhalation of aspergillus:

Clinical Evidence:

1. Appearance of symptoms at work and improvement when away from work.

2. Very severe bronchial symptoms during heavy exposure when near the mixers in operation, using rye flour as a duster, or when the shop is being swept.

Immunologic Evidence:

1. Negative skin reactions to all cereals.
2. Marked intradermal reactions to aspergillus and cephalothecium 100 pnu. The remaining mold tests were negative.
3. Significant skin reactions to six of the seven aspergillus species tested.
4. Positive reaction to aspergillus and cephalothecium on indirect testing (passive transfer). The remaining molds did not transfer. The cereals did not transfer.
5. No reaction following a sniff of talcum powder. A sniff of aspergillus powder initiated a very severe asthma attack, frightening in its intensity, within about fifteen seconds.
6. Aspergillus and other molds cultured on Sabouraud mediums from many parts of the shop.
7. Improvement after desensitization treatment with house dust, autogenous baker's dust and an aspergillus and cephalothecium mixture.
8. Further improvement after addition of a mixture of the positive reacting T 33 aspergillus extracts.

REFERENCES

1. Bonnevie, P.: Occupational Allergy in Bakery, Occupational Allergy. Springfield, Ill.: Charles C Thomas, 1958.
2. Tuft, Louis: Clinical Allergy. Philadelphia: Lea & Febiger, 1949.
3. Maunsell, K.: Respiratory Allergy to Fungus Spores. Progr. Allergy, Vol. 4. Basel, New York: S. Karger, 1954.

22-32 Radburn Road

METHODS OF SCIENCE

"The scientist is a practical man and his are practical aims. He does not seek the ultimate but the proximate. He does not speak of the last analysis but rather of the next approximation. His are not those beautiful structures so delicately designed that a single flaw may cause the collapse of the whole. The scientist builds slowly and with a gross but solid kind of masonry. If dissatisfied with any of his work, even if it be near the very foundations, he can replace that part without damage to the remainder. On the whole, he is satisfied with his work, for while science may never be wholly right it certainly is never wholly wrong; and it seems to be improving from decade to decade."—GILBERT N. LEWIS, *The Anatomy of Science*, Yale University Press.

ASTHMA SYNDROME ASSOCIATED WITH ANOXEMIA, HEPATIC AND RENAL INVOLVEMENT

Historical Document

JOSEPH HARKAVY, M.D.
New York, New York

A 46-year-old housewife was admitted to the Mount Sinai Hospital on February 12, 1943 in a state of coma of sixteen hours duration. It was said by members of the family that with the exception of a non-productive cough which began 14 months ago, the patient had had no previous illness. The cough disappeared for a short period, and about 8 months prior to admission she developed pain in the right side of the chest and fever. This was diagnosed as pleurisy and she was confined to bed for 2 months. She made a fair recovery but soon thereafter began to exhibit wheezing respirations suggestive of bronchial asthma. Adrenalin was ineffective in controlling the asthmatic attacks. Various skin tests failed to reveal an allergic etiology. Bronchoscopy did not disclose any abnormalities in the trachea or bronchi at the time of the examination. In September, 1942, she began to experience substernal pain which at first intermittent in character became progressively worse. On the evening of February 11th, 1943 when seen at her home she appeared to be in status asthmaticus. It was said that this condition began the day before when after a fit of coughing she suddenly developed dyspnoea, cyanosis and wheezing respiration. Inasmuch as the usual therapeutic measures such as epinephrine 1:1000, epinehrine in oil, etc. proved of no avail in controlling the symptoms, her physician administered 20 cc. of ether in oil, for the purpose of sedation. Although most of this was expelled, the patient went into a shock from which she recovered in about 30 minutes. On regaining consciousness she remained in the respiratory distress.

At this time on physical examination the patient appeared markedly cyanosed and gasping for breath. The respirations were shallow and rapid with a rate of 40-50 per minute. Her chest appeared distended and on percussion was tympanitic throughout. Auscultation disclosed generalized sonorous râles indistinguishable from those of true bacterial asthma. Her heart showed no abnormalities, but the pulse was rapid. She answered questions rationally although with difficulty, due to the embarrassment in her breathing. She pointed to the upper part of the sternum as the seat of the greatest discomfort.

In an attempt to give relief, she received within the space of two hours, ½ grain of papaverin, 100 mg. of nicotinic acid intravenously, 0.5

Reprinted by permission from *Journal of The Mount Sinai Hospital,* Vol. XII, No. 1, May-June, 1945.

cc. of epinephrine 1:1000, 1 cc. of epinephrine in oil as well as 10 cc. of aminophyllin intravenously without the slightest effect. The dyspnoea and the wheezing respiration continued even though oxygen was continuously administered through a nasal catheter. It was therefore decided that sedation was the treatment of choice and the patient was given 3 grains of seconal and 3 grains of sodium amytal by mouth. Following this she gradually became somnolent and lapsed into unconsciousness. The following day, February 12, 1943, she was brought to the Mount Sinai Hospital.

EXAMINATION

On admission she was in a stuporous state, with manifest cyanosis and wheezing respiration. Physical examination showed the neck veins distended, the trachea was shifted to the left and the respiratory movements of the left side of the chest were very much diminished. On percussion that side as compared with the right presented marked tympany both anteriorly and posteriorly. The resonance at the right base was impaired, on auscultation coarse râles and wheezing respiration were especially audible over the right lung. There was a diminution in the breath sounds over the left lung. The heart was in the normal position and the sounds were of good quality. The blood pressure was 100 systolic and 60 diastolic. The liver was palpable 2 fingers below the costal margin. The rest of the examination was negative except for absence of deep reflexes.

COURSE

The history of continuous wheezing and the shifting of the trachea to the left together with the restricted respiration of the left chest suggested the possibility of tracheal obstruction. Since the X-ray examination which was made immediately on admission showed no abnormality in the lungs, it was decided that she should be bronchoscoped. Bronchoscopy on this occasion disclosed a smooth lobular tumor ½ cm. above the carina. The mass moved from side to side and seemed to be sucked in alternately to the left and right main bronchus with each inspiration. The tumor appeared to arise from a broad base on the posterior wall of the trachea and proved to be readily removable with very little bleeding. Following this procedure the cyanosis and dyspnea which had persisted continuously for 36 hours, disappeared almost completely and the patient resumed normal breathing. At this time her temperature had risen to 104° F. and it was decided to give sulphathiazole prophylactically because of the possibility of a complicating pneumonia.

The following morning after only one gram of sulphathiazole had been given intravenously, the blood urea was found to be 36 mg per cent. The blood chlorides were 610, the CO_2 48 volumes per cent. The urine showed 2 plus albumin, the presence of urobilin 1:2, and a few hyalin and granular casts with a moderate number of red blood cells. The hemoglobin

was 68 per cent, the red blood cells 3.6 million. The white blood cells 10,950, with 75 per cent segmented polynuclear cells, 8 per cent nonsegmented, lymphocytes 15 per cent and monocytes 1 per cent.

In the belief that her comatose states, in spite of regular respirations, may have been due to barbiturate intoxication, although she had only received six grains in all (3 grains of seconal and 3 of sodium amytal), she was given 6 mgm. of picrotoxin intravenously. Following this she opened her eyes, appeared aware of environment but could not answer questions. The same dose of picrotoxin was repeated on four successive occasions but with no improvement. Throughout the nine days of hospitalization she never fully regained consciousness, except that occasionally she would open her eyes and look about blankly.

A neurological examination did not point to any localizing cerebral lesion. The neurologist, Dr. Joseph H. Globus, expressed the opinion that hypoventilation of the brain coupled with the sedation were probably responsible for the prolonged episode of unconsciousness. The electroencephalogram showed diffuse abnormal cerebral activity with no evidence of any focal lesion.

Treatment consisted of repeated intravenous injections of Ringer's solution with calcium gluconate, 10 per cent glucose and blood transfusions, all without any results.

After several days the patient developed fine râles at the base of the left lung, suggestive of pneumonic infiltration. Peculiar bulbous lesions appeared all over the body especially at points of pressure. The temperature remained at high levels ranging between 102° and 104° F. The pulse rate was between 110 and 140 beats per minute. The respiratory rate which had come down to 24 per minute after the removal of the tumor rose three days after admission to between 36 and 40 per minute. She developed edema of the face and back as well as chemosis of the conjunctivae. The urinary output decreased and the blood urea began to mount. Although the uremia had apparently begun before sulphathiazole had been administered in any appreciable quantity, it was thought advisable to exclude anuria due to blockage by sulphathiazole crystals. Cystoscopy, however, showed no evidence of obstruction and the urinary flow was present on both sides. The total output of urine increased somewhat following this procedure, but not to any marked extent. On the 17th of February, five days after admission, the total output of urine was 250 cc. in 24 hours. The specific gravity was 1014 and albumin was 2 plus. The blood urea nitrogen on February 14th, two days after admission, was 184 mg. per 100 cc. There was no rise in blood pressure which initially showed a systolic of 100 and a diastolic of 60. Three days before exitus there was a sudden appearance of icterus associated with hemorrhagic vesicles and numerous ecchymoses in various parts of her body. The patient showed distinct evidence of uremia and died on February 20th. It was the opinion

of Dr. Joseph H. Globus, who re-examined her two days before she died, that the cerebral symptoms were due to an encephalopathy secondary to transient anoxemia.

NECROPSY FINDINGS

The essential gross necropsy findings as reported by Dr. Paul Klemperer were as follows:

Trachea. On separating the esophagus from the trachea, a pyramidal tumor was encountered at the posterior and right lateral aspect of the trachea which was intimately connected with the tracheal wall. This measured 4 cm. in length and 2.5 cm. at the base. The tip of this mass was situated near the bifurcation of the trachea. It was well encapsulated, of brownish color and moderately soft consistency. Adherent to it was the vagus nerve. On the inner aspect of the posterior tracheal wall above the bifurcation at the same level as the external tumor mass, there was an area denuded of mucosa. In the base of this two cartilagenous rings were visible which showed irregular edges as if the terminal parts had been resected. In addition there were present marked acute pulmonary emphysema and edema of the lungs; bronchopenumonia at the right lower lobe; acute congestion of the liver, spleen and kidney, necrotizing inflammation of the lower half of the esophageal mucosa; multiple petechiae of the skin and small submucosal hemorrhages in both kidney pelves, bladder, colon and rectum; moderate hypertrophy of the right ventricle and subicterus. *Microscopic findings—trachea.* The tumor of the trachea was found to be an infiltrating cylindroma which ensheathed the vagus nerve.

Lungs. There was evidence of marked emphysema and bronchopneumonia in the right lower lobe. The rest of the lung showed congestion, edema and hemorrhages into the alveoli and bronchi.

Heart. There was intimal thickening of one coronary branch, otherwise no abnormalities were present.

Liver. The main finding consisted of severe congestion of the central portions of the sinusoids, atrophy and disappearance of central zone of liver cell cords and fatty infiltration of the liver cells in the periphery of the lobules. The cytoplasm of the liver cells showed fat globules together with clumps of bile pigment. The nuclei of many cells appeared to be breaking up into small round dark stained fragments.

Spleen. There was evidence of marked congestion and decrease in the lymphoid tissue.

Kidney. Congestion, edema and definite degeneration of the tubular

epithelium in the cortex with vacuolization and disappearance of cells appeared to be present. In addition there were degeneration of the tubular epithelium in the medulla and karyorrhexis with formation of numerous dark round fragments as well as submucosal hemorrhages of the calyces.

Brain. The scalp, calvarium and dura were negative. The leptomeninges were clear and glistening. Grossly the brain appeared normal although it was slightly softer than usual. The vessels at the base of the brain, the pituitary gland and the inner ears were negative.

On sectioning, the most striking lesion was found bilaterally and symmetrically within the globus pallidus which showed markedly reduced consistency, and was exceedingly friable with a greyish-red discoloration. This was evident in the most internal part of each globus pallidus. The lateral portions as well as the putamen seemed to be intact. Throughout the white substance of both cerebral hemispheres there were small punctate areas of discoloration which seemed to be either minute areas of red softening or areas of extravasation. These were also found within the middle cerebellar peduncle and the tegmentum of the pons.

Microscopic Description. "In the region of the globus pallidus there is a large area of very recent rarefaction. There is no apparent reactive phenomenon in the form of gliosis or inflammation. The cerebal cortex elsewhere shows no abnormality. With the Nissl stain, the aforementioned area noted in hematoxylin and eosin preparation shows complete cellular depopulation or else they have failed to stain. Patent vessels, although moderately sclerosed, are seen in this area. At the periphery there seems to be an increase in the number of glia; some of which are of the compound granular corpuscle variety."

Diagnosis. Encephalomalacia due to anoxemia in the region of the globus pallidus.

DISCUSSION

Under ordinary circumstances the presence of cough antedating true asthmatic seizures is a frequent occurrence. The original diagnosis of bronchial asthma in this patient was to a certain extent therefore justified, despite negative findings of allergy, especially since bronchoscopy six months prior to admission to the hospital did not reveal any obstructive lesion in the respiratory tract. The negative bronchoscopic findings were probably due to the fact that at the time of the examination the infiltrative lesion of the trachea was insufficiently pronounced to be detected. The bronchospasms responsible for the wheezing respiration simulating true bronchial asthma could therefore not have been due to tracheal obstruction as such, but in the light of the subsequent autopsy findings, to vagal irrigation induced by the infiltration of the cylindroma into and about the

vagus nerve. That stimulation of the vagus produces bronchial constriction is well known. The gradual invasion of the fibres of the vagus nerve, by tumor cells as observed microscopically, could therefore account for the irritation of this nerve with the resulting cough and the intermittent attacks of asthma in the early phases of the patient's illness, whereas the more or less complete investment of the vagus by the neoplasm would explain the continuous wheezing. The onset of so-called status asthmaticus, unusual in bronchial tumors, was probably due to the combined effect of sudden obstruction at the bifurcation of the trachea and the persistent bronchospasm induced by intense stimulation of the vagus nerve. The reason for the failure of various anti-asthmatic remedies to control the patients symptoms thus becomes patent. Obviously we were dealing with an "asthma syndrome" due not to edema and spasm of the bronchi on an allergic basis, but to an unusual form of bronchospasm caused by the mechanical and/or possibly chemical irritation of the vagus nerve by the infiltrating growth on the one hand, and intermittent bronchial obstruction by a pendulating mass on the other. This combination of factors proved to be responsible for the interference with the normal respiratory exchange and led to a progressive state of anoxemia. Under such circumstances six grains of barbiturates could be sufficient to accentuate the anoxic state in a brain whose oxidative functions were already depressed, and thus precipitate a state of coma. The ravages of oxygen deficiency were clearly demonstrable in the encephalomalacia observed in the region of globus pallidus.

Cerebral Changes Due to Anoxemia. That anoxemia may give rise to degeneration in the central nervous system has been shown by a number of investigators. A recent pertinent report by Suggs (1943) deals with the case of a 32 year old female patient who had been given 3 grains of nembutal, ⅙ grain of morphine sulphate, and 1/150 grain of atropin sulphate, prior to nitrous oxide anesthesia for an operation of an incomplete abortion. After 15 minutes of anesthesia, the patient ceased breathing. She was revived within an hour and lived for 41 days in a state of semiconsciousness with a temperature between 101° and 104° F. and pulse of 110 to 140. Various laboratory studies such as urine examination and blood chemistry were found to be negative. At autopsy the most striking finding consisted of cerebral and basal ganglia degeneration. The remaining organs showed moderate parenchymatous degenerative changes in the kidneys and liver in addition to a lung abscess in the lower right lobe.

Effect of Oxygen Deficiency on the Liver. The development of jaundice as a result of anoxemia has been studied by numerous workers, notably Rich and Resnik (1926); Rich, Bumstead and Barron (1930); Hesse (1942), Ladewig (1943), Monroe A. McIver (1943); Buchner (1942)

and others. Rich and his associates have demonstrated that simple anoxemia brings about not only atrophic shrinkage of the liver cells but also necrosis of the central liver lobules in the absence of heart failure and evidence of passive congestion in the lungs, spleen or any other organs. The cells about the efferent vein, in contrast to those in the peripheral region, are definitely more sensitive to the effects of a deficient oxygen supply, just as they are apparently more sensitive than the peripheral cells to the toxic effects of chloroform and other poisons. Rich and Bumstead have also shown that accompanying this liver damage is a concomitant depression of the excretory function of the liver so that its ability to excrete bilirubin injected into the blood stream is impaired. When necrosis of the central liver cells is sufficiently widespread the features of regurgitation jaundice appear because whole bile leaks into the blood from the broken canaliculi into the necrotic area. Similar liver changes have been described in various anemias and in cases of cardiac decompensation where anoxemia plays the dominant role in the development of a retention type of jaundice.

In airmen, who died as a result of anoxemia due to the effect of atmospheric conditions at high altitudes, Ladewig describes round or polyhedric vacuoles in the liver nearest to the acinous centers, which do not contain fat or glycogen. Corresponding alterations could be produced in guinea pigs and rabbits under atmospheric conditions similar to those at high altitudes by keeping animals in low pressure chambers under normal pressure, but reduced oxygen content of the respiratory air. Rossin (1928), for example, described parenchymatous degeneration and necrosis in the portions of the lobules in guinea pigs and rabbits subjected to low oxygen tension. Identical liver degeneration has been reported by Hesse in individuals thrown into an anoxemic crisis through suffocation or drowning.

Renal Changes due to Anoxemia. That oxygen want is also responsible for urinary suppression and uremia, the pathological substrate of which consists of tubular degeneration in the kidneys, has been demonstrated both clinically and at necropsy. The abnormal physiological effects upon the renal output in the case of a healthy male, who overbreathed for 45 minutes and failed to breathe again as he intended to do after the fifth time, has been reported by McCance (1935). In this clinical experiment acute anoxemia followed and was sufficiently severe to cause unconsciousness for about 3 minutes. The subject was in a state of collapse for two hours and recovered completely in three hours. During the period of synocope five samples of urine were collected and analyzed with results as follows: 1). The process of ammonia excretion and the ability to concentrate hydrogen ions was unimpaired. 2). The rate of excretion of creatinine and of sulphates were reduced respectively to three quarters and two thirds of their initial values. 3). The rate of excretion of urea was re-

duced to one fifteenth of its original value. "Part of this reduction may have been due to great increase in the excretion of ammonia." 4). The rate of excretion of water, sodium, potassium, chlorine and phosporus was reduced from one fifth to one fifteenth of their original values. 5). Urea clearance fell from 107 per cent of normal to 17 per cent during the period of collapse. It remained subnormal for three hours then rose to 114 per cent.

The theoretical explanation of these observations according to McCance is obscure, because not enough is known of the way urea, creatinine and sulphates are normally excreted and especially how the clearance of these three substances are related to true glomerular clearances. "The fall in the excretion rates of creatinine, urea and sulphates possibly other salt ions coupled with the probability that some fall of blood pressure took place suggest some fault in glomerular filtration."

The basis for the renal disturbances following anoxemia as above described becomes clearer, in the light of the necropsy findings in a series of cases who died from "crush injuries" in the bombing of London as recently reported by Bywaters and Beall (1941); Beall et al (1941); Mayon-Whyte and Solandt (1941); Glen (1941); Young and McMichael (1941) and others. The patients studied ranged in ages from 11 and upwards. The victims were rescued after having been buried for three or more hours under debris from devastated buildings. Some of them had sustained crush injuries to their legs and developed shock, whereas others with the exception of a hematoma in an extremity resulting from an overlying boulder presented no demonstrable injury either to the soft or skeletal tissues. After recovery, as a result of replacement of the circulatory fluids the majority of patients developed oliguria, smoky urine and edema. Death in uremia, with markedly elevated blood urea, followed after about a week in most instances, some few however recovered.

In this connection the clinical and pathological findings in a girl, 11 years of age, pinned under debris for three hours are of pertinent interest. Complete examination in this patient revealed no injury except for a hematoma. She was drowsy, manifesting pitting edema from hip to toes and almost complete anuria except for a few cc of urine. In spite of treatment the blood proteins decreased from 6.4 to 4.8 mg. The blood pressure rose to 145 systolic and 110 diastolic and the blood urea to 399 mg per 100 cc before death. The temperature remained subnormal throughout. At autopsy most of the tubules contained a peculiar debris that stained a brick red color with eosin. The tubules showed marked degeneration, and some of the cells lost their outlines completely. The glomerulae were normal and the capsular spaces were not dilated. In the cases reported by Bywaters, the degenerative changes took place in the proximal convoluted tubules and pigment casts were present in more distant parts. The lungs showed focal hemorrhages and patchy edema,

while the liver displayed parenchymatous degeneration and edema in the region of the portal system with dilated lymphatics.

The question whether an unidentified toxic derivative from crushed or necrotic muscles is responsible for the renal damage observed in these cases is excluded by Tomb (1942) on the following grounds: 1). The symptoms of renal insufficiency appear early, and are progressive even though the crushed limb is amputated. 2). They are found in cases where no crushing of muscles has occurred. 3). They do not occur as a sequel of infarction or absorption of blood clot (tissue necrosis). 4). It is impossible to establish by cross circulation or other methods, that the blood of an animal suffering from crushing of the limbs (traumatic shock) is toxic. (Mc Dowell, 1940).

Manifestations due to anoxemia similar to the renal failure of crush injury, with comparable degenerative changes in the envoluted tubules, which persisted after successful restoration of the circulation by saline infusion, have also been reported by Tomb in association with the anuria in cholera.

It is evident therefore as a result of these observations that oxygen deficiency may induce pathological changes in various organs. In the brain such alterations may be characterized by encephalomalacia, in the liver by a central necrosis of the liver cells, and in the kidney by tubular degeneration. Such tissue changes may be responsible for development of coma, jaundice, anuria and uremia. The presence of similar manifestations in the case under discussion, supported by the post-mortem evidence of encephalomalacia in the region of the globus pallidus, the degeneration of the central zone of the liver cords and tubular epithelium in the cortex and medulla of the kidneys, is strongly suggestive, in the absence of any other etiologic factor, that anoxemia was the most probable cause of this clinical picture. The possibility that the hepato-renal damage may have been caused by the sulphathiazole is unlikely inasmuch as the 1 gm. administered was too small a dose to cause such extensive injury to various organs unless the question of hypersensitiveness to this drug were involved. Inasmuch as there was no history of any drug idiosyncrasy in this case and no authentic record in the literature of similar tissue damage on the basis of sulphathiazole allergy to so small a quantity of this drug, this possibility may be ruled out. Moreover, since the patient had been in coma at least sixteen hours prior to her admission to the hospital the anoxemia antedated the administration of sulphathiazole by twenty-four hours if not longer.

SUMMARY

A 46-year-old housewife presenting symptoms suggestive of status asthmaticus developed coma following the administration of 3 grains of seconal combined with 3 grains of sodium amytal.

Necropsy revealed 1) a pedunculated cylindroma of the trachea, ensheathing the vagus nerve; 2) encephalomalacia in the region of the globus pallidus; 3), central necrosis of the liver cords, and 4) tubular degeneration of the kidneys.

The abnormal alterations in the brain, liver and kidneys were regarded as the results of anoxemia which accounted for the coma, jaundice and renal insufficiency manifested by the patient.

The anoxemia was induced by interference with respiratory exchange consequent upon bronchospasm due to irritation of the vagus by the infiltrating cylindroma on the one hand and intermittent broncho-obstruction by the pedunculated segment of the tumor on the other. It was furthermore accentuated by the barbiturates.

The combined effect of broncho-constriction and mechanical obstruction of the bronchi was responsible for the asthmatoid and status-asthmaticus like state.

THEORIES ARE LIKE A STAIRWAY ENDING

Theories are like a stairway; by climbing, science widens its horizon more and more, because theories embody and necessarily include proportionately more facts as they advance. Progress is achieved by exchanging our theories for new ones which go further than the old, until we find one based on a larger number of facts. In the case which now concerns us, the question is not one of condemning the old to the advantage of a more recent theory. What is important is having opened a new road; for well-observed facts, though brought to light by passing theories, will never die; they are the material on which alone the house of science will at last be built, when it has facts enough and has gone sufficiently deep into the analysis of phenomena to know their law or their causation.—Claude Bernard, 1813-1878—from the *Introduction to the Study of Experimental Medicine.* (In *Moments of Discovery. The Development of Modern Science.* Edited by George Schwartz and Philip W. Bishop, New York Basic Books, Inc., 1958.)

Editorial

The opinions expressed by the writers of editorials in the ANNALS *do not necessarily represent the group opinion of the Board or of the College.*

WITH WHAT WE MUST CONTEND

The blood of a patient who has never, by any type of skin or provocative test, demonstrated any inhalant or food allergy was sent to a laboratory which, by means of "sero diagnosis" furnishes unwary physicians with diagnoses and suggestions for treatment. The note returned by the laboratory stated that the patient suffered from frequent bouts of lower respiratory tract infections. Chocolate was suspected as being the cause of the exacerbations.

The following report is printed unchanged as regards "strep.", "staph." and "dust bacteria". Neither emendations nor corrections have been made in the instructions for food elimination, sugars, food diary, frequent offenders, infections, inhalants (dust) as well as dust treatment. The grammatical errors such as person, number, gender, case and syntax have not been corrected. The italics have been reproduced exactly as the writer of the report placed them. Those lists of substances for which no positive reactions were reported have been omitted for the purpose of saving space. But all of the substances contained in any group, in which positive reactions have been noted, are included in the present reproduction in order to emphasize the inconsistancies involved in the list of forbidden vegetables, sugars and forms of milk. All of the foods included in the lists characterized by a check mark were not to be eaten. These are presented in linear rather than in columnar form, although following the list of "Processed Meats", the note "Grind or cube meat at home" was encircled.

The patient has never suffered from any symptoms no matter how many of the foods listed have been eaten or in whatever quantity.

No improvement followed the injections of "our strep. and staph. vaccine". Nor was improvement noted after the six months course of "oral dust desensitization".

Except for the deletion of the names of the physician and the patient, as well as the date (1960), the report reads as follows:

His allergy survey indicates a pronounced dust allergy, important food allergies, complicated at this time by infection. Many of our physicians are finding our strep. and staph. vaccine of much benefit to their patients carrying infection. May we send you a vial of this vaccine? The strength of this vaccine is determined by the degree of infection as is indicated in the patient's survey.

His pronounced dust allergy indicates that all dust precautions, as are listed on the back of his report sheet, are of much importance as well as extended treatment. Our oral dust hyposensitization is also made up in strength of dosage according to the

degree of allergic sensitiveness as is indicated in the survey, and comes to you in three containers of graduated strengths. These three containers are sufficient for a six-month supply. May we send you the first six-month treatment for the patient?

He has many important food allergies, all of which, even the latent, should be eliminated from his diet for an extended period, as his symptoms are chronic. After infection has been controlled and major allergies overcome, it may be possible to return the lesser of his allergic foods to his diet, one at a time, according to your judgment, watching for possible recurrence of symptoms.

You will note that cornmeal and popcorn are circled in red, not because of a corn allergy, but because these two products usually carry much of the dust bacteria to which he is sensitive, and would not be well-tolerated by him. The same holds true for tomato paste, as it has been found that commercially-canned tomatoes which usually contain overripe tomatoes are not well-tolerated by the allergic patient, even when they do not show an allergy to fresh tomatoes. It is well that chocolate has been eliminated from his diet, and as he improves, raw fruits and green vegetables may agree with him. We find no allergies there. (The appended list shows no evidence in red of cornmeal or popcorn, Editor's note.)

As this patient's symptoms are not constant, he may think that cooperation with you at all times is not necessary. This, however, is not true if he expects to build lasting resistance. He may be one of many patients who has a naturally high allergic resistance and only demonstrates symptoms when resistance is lowered, as in this instance, by infection. It is hoped that he will cooperate fully with you and not expect results too soon.

If there are further questions, or we can be of help in any manner, please feel free to contact us.

Food Elimination.—A food marked plus or latent should be entirely eliminated from the diet. After improvement, it may be possible to restore the latents, one at a time, watching for possible return of symptoms. Should symptoms recur, these foods should again be withheld. The chronic patient usually requires extended dietary control. The patient with seasonal symptoms frequently discounts the importance of diet control.

If a food has been partially or totally withheld before testing, a latent or one plus demonstrates extreme sensitiveness, possibly a "fixed allergy". Such a food should be withheld indefinitely.

Sugars.—Patients sensitive to unrefined sugars, namely brown sugars and molasses, should use refined white cane sugar, such as Dixie Crystals, Domino, and Hershey. Patients sensitive to cane sugar may substitute corn sugar, beet sugar, honey, or maple.

Food Diary.—Until marked improvement is noted, a daily food diary, including symptoms, for the physician's review has been found to be of much value. Many patients make mistakes in diet without realizing same and small deviations can be of much consequence. A mistake in diet will usually be found in the three or four meals previous to onset of symptoms. Symptoms may not manifest themselves with every break in diet, which often misleads the patient. Full cooperation from the patient is necessary if good results are to be obtained.

Frequent Offenders.—Some foods are frequent offenders, in varying degrees of sensitiveness, such as chocolate, processed and commercially ground meats, unrefined sugars and malt, cheese and the soured milks, sauerkraut, tomato paste, dried fruits, beer, wine, corn meal and popcorn. These foods usually contain bacteria as are found in dust and are of major importance whatever the symptoms may be. Cooking kills these bacteria but the offending toxin remains and can produce symptoms.

EDITORIAL

Infection.—Infection is associated with many allergic diseases and retards progress. Therefore, when infection is found to be present, *treatment is indicated.* Intestinal infection from allergic foods may be present even though blood counts are within normal range. When infection complicates procedures, progress should not be expected too soon. This is especially true of the asthmatic and the difficult allergic skin disorders.

Infection usually raises the titer of a report. Therefore, when infection is present, a latent allergy may be of less consequence.

Inhalants (Dust).—Dust sensitivity has been found to be a major inhalant problem. Dust control in the patient's home and working environment *is imperative.* Dust precautions are listed on the back of the report sheet. Contact with dusty areas should be avoided. If dust avoidance is impossible at times, a mask should be worn. Folded gauze tied about the head, covering both nose and mouth and dampened over the breathing area, is adequate.

Dust Treatment.—Oral dust hyposensitization treatment is usually of much benefit to the dust sensitive patient. This oral treatment, sufficient for six months, is supplied in three bottles of graduated strengths, the strengths being determined by the individual patient's sensitiveness as demonstrated in his allergy report. However, occasionally a patient is encountered who cannot take the indicated dosage. Should this occur, another first bottle (#1-A) of further dilution is furnished free of charge. *Extended treatment* may be necessary for the chronic dust sensitive patient. This according to the physician's judgment.

Avoid all foods, inhalants, etc. marked plus One Plus + Two Plus ++ Three Plus +++ Four Plus ++++	
L—Latent—Eat occasionally when free of symptoms	
Foods, inhalants, etc. marked negative (—) indicate no allergy.	
MILK	
Buttermilk	++
Cheese (All Types)	+++
Cow's Milk—Sour	++
" " Sweet	—
Goat's Milk	+
Junket	++
Yogurt	+++
BEVERAGES	
Chocolate—Cocoa	+++
Coffee	—
Tea	—
Colas	—
Ginger Ale	—
Grapette	—
Root Beer	—
Seven Up	—
Ale	+++
Beer	+++
Bourbon	+
Gin	+
Rye	+
Scotch	+
Vermouth	+
Wine	+
VEGETABLES	
Asparagus	—
Beans—Baked	+++
" Dried	+

" Lima	—
" Soy	—
" String	—
Beets	—
Broccoli	—
Brussels Sprouts	—
Cabbage	—
Carrots	—
Cauliflower	—
Celery	—
Chinese Cabbage	—
Chives	—
Collards	—
Corn	—
Cucumber	—
Endive	—
Eggplant	—
Garlic	—
Lettuce	—
Mustard	—
Okra	—
Onion	—
Parsley	—
Peas—Black-eyed	—
" Green	—
Peppers	—
Potatoes—Sweet	—
" White	—
Pumpkin	—
Radish	—
Rhubarb	—
Rutabaga	—
Spinach	—
Squash	—
Sauerkraut	+++
Tapioca	—
Tomato—Fresh	—
" Paste	+++
Turnip	—

SUGAR - SYRUPS	
Cane—Granulated	—
" Brown	+++
" Confectionery	—
" Molasses	++
" Powdered	—
Corn Sugar	—
Honey—Clover	—
" Orange	—
Karo	+++
Malt	+++
Maple	—

MISCELLANEOUS	
Caroid	—
Flaxseed	—
Glue	—
Mint	—
Vanilla	—
Vinegar—Apple	—
" Malt	+++
" White	—

INHALANTS - CONTACTANTS	
Cotton Linters	—
Dander—Cat	—
" Dog	—
" Horse	—
" Rabbit	—
Dust	+++
Feathers—Chicken	—
" Duck	—
Orris	—
Rice Powder	—
Tobacco	—
Wool—Lanolin	—

BEEF

Often Found in:

Veal
Beef Liver
Beef Tongue
Bouillon
Chili
Cold Cuts
Consomme
Corned Beef
Fresh Beef
Gelatin
Hot Dogs
Jello
Meat Balls
Sausages (Some)
Soups (Some)
Tamales
Tripe

PROCESSED MEATS

Often Found in:

Bologna
Canned Meats
Chili
Corned Beef
Cured Ham
Hamburgers
Hot Dogs
Liver
Livercheese
Meats Ground or Cubed at Market*
Pizza Pie
Sausage
Smoked Meats
Sugar Cured Bacon
Tamales

*Grind or cube meat at home

MALT

Often Found in:

Ale
Beer
Breads
Cookies
Crackers
Dextrose-Maltose
Frozen Malts
Malted Milk
Prepared Cereals (Many)
Syrups
Vinegars (Some)
Zwieback

Cereals Not Malted Are:—

Shredded Wheat (large)
Puffed Wheat (plain)
Puffed Rice
Cheerios
Cooked Cereals

THE VALUE OF SCIENCE

But sometimes truth frightens us. And in fact we know that it is sometimes deceptive, that it is a phantom never showing itself for a moment except to ceaselessly flee, that it must be pursued further and ever further without ever being attained. Yet to work one must stop, as some Greek, Aristotle or another, has said. We also know how cruel the truth often is, and we wonder whether illusion is not more consoling, yea, even more bracing, for illusion it is which gives confidence. When it shall have vanished, will hope remain and shall we have the courage to achieve? Thus would not the horse harnessed to his treadmill refuse to go, were his eyes not bandaged? And then to seek truth it is necessary to be independent, wholly independent. If, on the contrary, we wish to act, to be strong, we should be united. This is why many of us fear truth; we consider it a cause of weakness. Yet truth should not be feared, for it alone is beautiful.—HENRI POINCARE, 1859-1912. Translated by G. B. Halstead (From *Moments of Discovery,* Volume 2 of *Origins of Science,* George Schwartz and Philip Bishop, Basic Books, New York, 1958.)

Papers of Interest

Higgins, I.: Tobacco smoking, respiratory symptoms and ventilatory capacity. Brit. J. Med., 5118:325-329 (Feb. 7) 1959.
Smokers, as compared to non-smokers, suffer from more lung illness, wheezing, dyspnea, "chronic bronchitis" and lower maximum breathing capacity.

Tuft, L.: House-dust as a factor in allergic eczema (atopic dermatitis). Clin. Med., 6:201-205 (Feb.) 1959.
The author reviews his previous work in eliciting atopic dermatitis with inhalation of micronized powdered house dust allergen. Desensitization is similar to that used in respiratory tract allergy, although the first doses must be highly diluted.

Kress, M.: Broncholithiasis. Clin. Med., 6:183-191 (Feb.) 1959.
Although cough is the most frequent symptom in asthmatoid wheeze, it may be sufficiently severe to simulate recurrent or even intractable asthma.

Arbeiter, H.: Pediatric allergy, recognition and management. Clin. Med., 6:215-218 (Feb.) 1959.
A review which discusses pyloric stenosis, allergic rhinitis, eczema, common pediatric types of food allergy; their prevention and treatment.

Unger, D. L., and Unger, L.: Repository treatment in allergy. Illinois M. J., 116:99, (Aug.) 1959.
Widely quoted optimistic discussion of potentiality of injection treatment by means of emulsified pollen extracts.

Seltzer, A.: The "one-shot" hay fever treatment—facts and fancy. Med. Ann. District of Columbia, 28:436 (Aug.) 1959.
Although out of date on the basis of noting that injections of emulsified extract need to be multiple and that patients must be observed for four to five hours, an impartial review.

Siegel, S. C., Lovin, B. J., Ely, R. S., and Kelley, V. C.: Adrenal function in allergy III. Effect of prolonged intermittent steroid therapy in allergic children. Pediatrics, 24:434 (Sept.) 1959.
In forty-two severely allergic children who had not responded favorably to the usual types of treatment, there was an excellent response in eleven and a good effect in twenty-eight with poor effects in only those when all received prednisolone administered intermittently.

Johnstone, D. E.: Study of the value of bacterial vaccines in the treatment of bronchial asthma associated with respiratory infections. Pediatrics, 24:427 (Sept.) 1959.
Addition of bacterial vaccine therapy to usual treatment of asthma including specific hyposensitization had no appreciable beneficial effect. In sixty children as compared with fifty-eight control patients studies for three and one half years, the addition of vaccines of bacteria showed no beneficial effects.

Finke, W.: Chronic pulmonary diseases in patients with lung cancer. New York State J. Med., 58:3783, 1958.
Of eighty-six patients with lung cancer, fifty-six suffered from preceding chronic bronchitis, often associated with chronic asthma or suspected tuberculosis. In six, chronic pulmonary tuberculosis had been present for ten or more years. Silicosis affected one and lung damage from gas poisoning, two others. In sixty-eight, there was a history of pneumonia or influenza.

Plymyer, R. E.: Cottonseed allergy. Med. Bull. University of Michigan, 25:220 (June) 1959.
According to the author, "cottonseed remains a potent but infrequent offender in clinical allergy; should be increased interest in the potentialities of this allergen in the current widespread use of cottonseed flour in foodstuffs."

PAPERS OF INTEREST

Good, T. A., Benton, J. W., and Kelley, V. C.: Symptomatology resulting from withdrawal of steroid hormone therapy. Arthritis & Rheumat., 2:299 (Aug.) 1959.
In rheumatic patients, the rebound phenomenon and the toxic reactions with serious consequences are emphasized.

Herbert, C. C.: Uses and abuses of bronchial positioning. Kaiser Foundation Med. Bull., 7:185 (July-Sept.) 1959.
A clear concept of segmental anatomy provides a rational basis for postural drainage. The bronchi and lobar segments are indicated diagrammatically and as they appear on the upright roentgen films of the normal chest.

O'Connor, F. M.: Recent concepts of pruritus and eczema. Am. Practitioner, 10:1004 (June) 1959.
Present-day concepts relative to pruritus based on recent biochemical and physiologic research.

Castro, I. M.: Serious considerations in the use of the suprarenal hormones. Arch. de Hospital Univ., Havana, 11:46 (Jan.-Feb.) 1959. (In Spanish.)
Excellent review.

Sjoerdsma, A.: Serotonin. New England J. Med., 261:181 (July 23) 1959.
Best and most complete review available.

Takeda, Y.: On the biological functions of tissue mast cells in the salivary gland. Bull. Yamaguchi Med. School, 5:103 (Dec.) 1957.
Blood level histamine is low when much saliva is excreted. Salivary gland mast cells replenish body histamine.

Downing, J. G.: Dermatology. New England J. Med., 260:1170 (June 4) 1959.
Should be read for review of contact dermatitis and of dermatologic manifestations of drug reactions.

Brogen, N., Duner, H., Hamrin, B.: Urticaria pigmentosa (mastocytosis): a study of nine cases with special reference to the excretion of histamine in urine. Acta med. scandinav., 163:223, 1959.
All nine showed abnormal histaminuria but no increase in 5-hydrocyindoleacetic acid. One patient responded to aspirin ingestion with anaphylactic shock and signs of histamine release.

Velasco, H. A., and Sokal, J. E.: Cholestatic jaundice in association with desacetylmethylcolchicine (Colcemide). Report of a case. New England J. Med., 260: 1280 (June 18) 1959.
A case of intrahepatic cholestatic jaundice of the so-called "chlorpromazine type" after the administration of desacetylmethylcolchicine to a patient with myelocytic leukemia is presented.

Prausnitz, C.: Past and Present: The passive transfer in allergy. Muench. med. Wochnschr., 100:1313, 1958. (In German.)
Lecture on history and present state of the passive transfer in allergy.

Koelsch, F.: Foam rubber causes no contact dermatitis. Muench. med. Wochnschr., 100:1233, 1958. (In German.)
Occasional allergic reactions were observed in persons occupied in the manufacture of foam rubber from synthetic polymers. No reactions have been reported with the use of finished foam rubber products.

Angelakos, E. T., and Loew, E. R.: Influence of histaminase inhibitors on certain pharmacological effects of histamine. Pharmacodynamie, 117:277 (Nov.-Dec.) 1958.
Histaminase plays no part in the pharmacological reactions to histamine.

Ehrlich, R. M.: A neurological complication in children on phenothiazine tranquilizers. Canad. M.A.J., 81:241 (Aug. 15) 1959.
A characteristic neurological syndrome of generalized skeletal muscular spasm may follow the use of phenothiazine compounds used ataractically.

Juel-Jensen, B. E.: Sensitivity to phenindione. Report of a case of severe diarrhoea. Brit. M. J., 2:173 (Aug. 15) 1959.
Steatorrhoea developed during the seventh week of phenindione administration in a sixty-seven-year-old male patient suffering from peripheral vascular disease.

PAPERS OF INTEREST

Schwartz, T. A., and Slasman, W. H.: Nasal decongestion with a new oral preparation: preliminary report. Eye, Ear, Nose & Throat Month., 38:645 (Aug.) 1959.
In thirty-five patients, a tablet containing chlorprophenpyridamine maleate, phenindamine tartrate and phenylpropanolamine HCl taken orally twice daily is reported as an effective decongestant. Side effects and rebound phenomenon were not observed.

Davis, T. W., Kerr, R. B., and Bogoch, A.: Experience with glipasol (R.P. 2259)—an antidiabetic sulfondamide drug. Canad. M.A.J., 81:101 (July 15) 1959.
In 54 per cent of the patients given 2-sulfamido-p-aminobenzene -5-ter-butyl-1,3,4-thiadiazole, hepatic dysfunction occurred. By biopsy (in five patients) portal and periportal inflammation was discovered.

Feigen, G. A., Trapani, I. L., and Hurd, M. S.: Immunological behavior of papain-treated erythrocytes. I. Specific agglutination and sedimentation. J. Infec. Dis., 104:253 (May-June) 1959.
The enzymatic action of papain unfolds or exposes reactive sites of protein molecules and so may increase the interaction between the cell surface and specific and nonspecific bonding agents.

Rainey, R. L., and Deutsch, D. L.: Allergy to effort. Ann. Int. Med., 51:162 (July) 1959.
Effort-induced angiodema and urticaria, apparently true physical allergy.

Fuchs, A. M., and Maurer, M. L.: Clinical evaluation of parabromdylamine maleate in patients with respiratory allergies. New York State J. Med., 59:3060 (Aug. 15) 1959.
Labeled as outstanding for symptomatic relief. Few side reactions encountered.

Hampton, O. P., Jr., and Hard, J.: Active immunization against tetanus with intradermal toxoid. Surg., Gynec., & Obst., 109:223 (Aug.) 1959.
Suggests that with the intradermal injection of the aluminum phosphate-absorbed tetanus toxoid, a degree of active immunity can develop in seven to ten days.

Duchaine, J., Spagen, R., and Jacques, M.: The new corticosteroids (methylprednisolone, triamcinolone, dexamethasone) in the treatment of bronchial asthma. A comparison with prednisone. Study of 145 cases. Presse med., 67:1386 (July 11) 1959.
Comparative studies in 145 patients.

Graham, J. B., and Graham, R. M.: The effect of vaccine on cancer patients. Surg., Gynec. & Obst., 109:131 (Aug.) 1959.
Autogenous vaccine from the malignant growth in Freund's adjuvant was administered to patients suffering from advanced disease. Of those who survived for more than one month, fourteen of 101 were free of disease for seven to thirty months or more. More than half lived longer than seven months.

Long, D. A.: Immune and allergic reactions to diphtheria toxin and toxoid in guinea pigs. J. Hyg., 57:216 (June) 1959.
In guinea pigs hypersensitivity to both toxin and toxoid was noted, the former causing an immediate Arthus phenomenon which increased with increase in circulating antibody, and the latter a delayed or tuberculin type of reaction.

Loev, B., and Dawson, C. R.: Synthesis of urushenol, the mono-olefinic component of the allergenic principles of poison ivy and Japanese lac. J. Org. Chem., 24:980 (July) 1959.
The synthesis of the olefinic catechols makes future clinical studies a more exact procedure.

Schwartz, H.: The comparative effects of corticotrophin (ACTH) and steroids in hormonal treatment. Canad. M. A. J., 81:159 (Aug. 1) 1959.
Dose levels of corticotrophin injected daily are recommended as safe for indefinite periods of treatment.

In Memoriam

DAVID R. BARGLOW, M.D.

Dr. David R. Barglow of Trinidad, Colorado, was born in 1907 in Augustow, Poland. He received his secondary education in Dresden, Germany. Dr. Barglow took his pre-medical work at the Wurzburg and Breslau Universities, his medical work at the Universities of Dusseldorf and Marburg, and received his degree of Doctor of Medicine in 1933. Later, he did research work in tuberculosis at the Swiss Research Institute in Davos and at the Forlanini Institute in Rome, Italy. After coming to the United States in 1938, Dr. Barglow practiced in Westcliffe, Colorado. He then practiced for sixteen years in Trinidad, Colorado.

Dr. Barglow wrote numerous scientific papers, his last paper being presented at Nassau at the First Bahamas Conference.

He was a member of the Academy of Psychosomatic Medicine, the American Writers' Association, the Colorado Society of Internal Medicine, the Colorado Heart Association, the Colorado Trudeau Society and the American Medical Association.

Dr. Barglow became a member of The American College of Allergists in 1951.

L. U.

JACK STERNBERG GOLTMAN, M.D., F.A.C.A.

Dr. Jack Sternberg Goltman died on August 7, 1960, at his home in Memphis, Tennessee.

Dr. Goltman received his Bachelor of Science Degree from Pennsylvania University in 1925 and his Doctor of Medicine from Cornell University in 1929.

Among the associations to which he belonged were the Mid-South Allergy Forum, Southwest Allergy Forum, Memphis and Shelby County Medical Society and the Tennessee State Medical Society. In addition to his practice, Dr. Goltman was an instructor at the University of Tennessee.

Dr. Goltman was promoted to Fellowship in The American College of Allergists in 1947.

Scientific Understanding and Human Understanding

"Strictly speaking, science cannot offer understanding of any individual case; and human understanding does not grasp the common elements among different cases. Science depends on the intellectual abstraction of similarities, classes and expanding generalizations. Human understanding depends on sympathetic insight into what is special, individual, unique.

"In other words, there is a tremendous difference between the meaning of 'understanding' as used for science and the way it is used for personal relationships. So far, at least, science is only partially successful. It deals with selected aspects of the total person. No unified 'science of the whole person' exists. Scientific understanding is selective, fragmentary and abstract."—Morris Philipson.

News Items

THE AMERICAN COLLEGE OF ALLERGISTS

Membership Directory—Interim Addendum

New Active Fellow

HOLMAN, James, M.D.
1405 Medical Arts Building
Dallas, Texas

New Associate Fellows

ADAMS, Myron J., M.D.
Doctor's Building
Kingsport, Tennessee

BEIRNE, Gilbert A., M.D.
20 Genevra Road
Hillsborough, California

BOLINSKE, Robert E., M.D.
950 Francis Place
Clayton, Missouri

FISCH, Ben R., M.D.
Duke University Hospital
Durham, North Carolina

KROEGER, Carl B., M.D.
611 West Market Street
Akron 3, Ohio

McCORMICK, R. Richard, M.D.
60 Orange Street
Bloomfield, New Jersey

ORTEGA, Carlos R., M.D.
2136 Lincoln Park West
Chicago, Illinois

SCHNITZKER, Wm. F., M.D.
700 13th Street
Lexington, Kentucky

SPARKS, Paul R., M.D.
102 West Broad Street
Burlington, New Jersey

STRICK, Lawrence, M.D.
16550 Ventura Boulevard
Encino, California

STROMBERG, Samuel, M.D.
1730 University Avenue
Bronx
New York, New York

TRUSS, Claude Oran, M.D.
1211 27th Place South
Birmingham, Alabama

Dependable Clean Dry Pollens and Powdered Allergens

POLLENS-DRIED or DRIED AND DEFATTED
More than 200 species—Correctly named
POWDERED ALLERGENS—DRIED AND DEFATTED
More than 450 items—Including Epidermals—Foods—Dusts—Insects—Molds—Miscellaneous
Reasonable Prices *Write for Price Lists*

C. G. BLATT & COMPANY
10930 E. 25th Street, Independence, Mo.
Phone: Clifton 4-5948

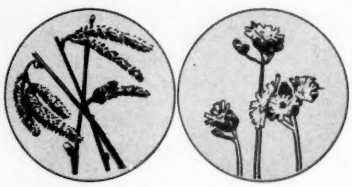
POLLENS:
200 species, thoroughly dried, correctly named.
POWDERED ALLERGENS:
Epidermals, foods, dusts, insects, molds and miscellaneous allergens.
DISTRIBUTION MAPS:
Of all the important hay fever plants of the U. S.
KODACHROME PICTURES:
2" x 2" color slides of all the important hay fever plants.
WRITE FOR PRICE LISTS AND LITERATURE

STEMEN LABORATORIES, INC.
Box 6306 **Oklahoma City 11, Okla.**

when an antihistamine alone is not enough... 'ACTIFED'®

ANTIHISTAMINIC • DECONGESTANT

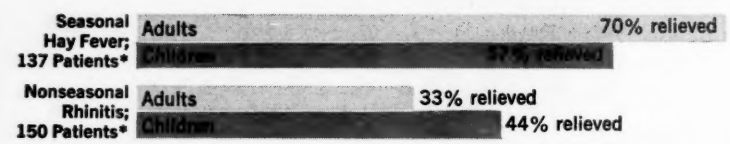
relieves the sneeze, wheeze, and other symptoms of HAY FEVER and ALLERGIES



- **effective in low dosage**
- **safe even for the youngest children**

Combining 'Actidil' (an antihistamine of unusually high potency) with 'Sudafed' (an orally effective nasal decongestant), 'ACTIFED' is "effective in a significant percentage of cases of seasonal and nonseasonal allergic rhinitis failing to respond to antihistamines alone."[1]

good to excellent results in rhinitis previously resistant to antihistamines



Prescribe safe 'ACTIFED' in tablet form or as a pleasant-tasting syrup:

Each scored tablet contains —

'Actidil'® brand Triprolidine Hydrochloride..... 2.5 mg.

'Sudafed'® brand Pseudoephedrine Hydrochloride.. 60 mg.

Each 5 cc. teaspoonful of the syrup contains —

'Actidil' brand Triprolidine Hydrochloride ..... 1.25 mg.

'Sudafed' brand Pseudoephedrine Hydrochloride. 30 mg.

DOSAGE: (may be given 3 times daily, or, because 'Actifed' has such a wide margin of safety, may be adjusted to provide optimal therapeutic effect in stubborn cases)

	Tablets	Syrup
Adults and children over 6 years	1	2 tsp.
Children 4 months to 6 years...	½	1 tsp.
Infants up to 4 months.....	—	½ tsp.

(While pseudoephedrine causes virtually no pressor effect in normotensive patients, it should be used with caution in hypertensives; and although triprolidine hydrochloride has an unusually low incidence of antihistaminic drowsiness, appropriate precautions should be observed.)

1. Feinberg, S. M., Feinberg, A. R., and Fisherman, E. W.: J. Indiana M. A. 52:2137 (Dec.) 1959.
*Adapted from authors' table.

BURROUGHS WELLCOME & CO. (U.S.A.) INC., Tuckahoe, New York